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A Framework of Ontology-Based Tablet Production Supporting System for a Drug Reformulation

Nopphadol CHALORTHAM[†a)], **Phuriwat LEESAWAT**[†], **Taneth RUANGRAJITPAKORN**[††], ***Nonmembers***, ***and*** **Thepchai SUPNITHI**[††], ***Member***

SUMMARY This paper presents a framework of supporting system for a drug formulation. We designed ontology to represent the related knowledge for reusable and sharing purposes. The designed ontology is applied with operation rules to suggest an appropriate generic drug production based on information of original drug. The system also provides a validation module to preliminarily approve a pharmaceutical equivalence of the suggested result. Preliminary testing with four random samples shows potential to reformulate a generic product by returning a satisfactory and acceptable of the system suggestions for all samples.

key words: *ontology, generic drug production, tablet production supporting system, drug formulation*

1. Introduction

Generally, a new invented original drug is legally protected from imitation by its patent. Once a patent of an original drug is expired, a generic version of the drug can be instantly developed by other drug companies. Normally, a cost of generic products is particularly lower than the market price of the original brand-name products since the generic production does not involve in an investment in a drug discovery and a full clinical test standard. With its low cost, a generic drug product becomes a demanded product in pharmaceutical market for daily usage. In fact, a generic drug is reformulated based on the details given in the original drug patent. Five years are generally consumed in a generic drug development. Especially, a laboratory development phase consumes around 25% from the entire development cycle [1]. Time consuming in a laboratory development phase is caused by implicit details in an original drug patent. The implicit information includes a crystal form of ingredients, an amount of excipients and a functional type of excipients. Moreover, a necessary factor in a generic drug reformulation certainly is a pharmaceutical equivalence between a generic drug and an original drug. In laboratory evaluation, it is mainly focused in generic drug development to primarily control a generic drug quality.

Despite many dosage forms of drug, tablet is the most preferred and widely used dosage form among other because of its stability, long life measured in years, easiness of transportation, and simple consumption. Moreover, a tablet dosage form covers over 80% of drug market [2]. Hence, this research focuses on a production of generic tablet formulation. One question raised in this research is *how to reformulate a generic tablet based on information given in an original drug patent effectively*.

A generic tablet reformulation is a re-engineering process using only information of an active ingredient, excipients and characteristics of the original product [3]. It is fundamental to define an explicit knowledge related to tablet production. An ontology is exploited to represent knowledge of a pharmaceutical tablet production. It is a backbone of knowledge that emulates expert thought to solve generic reformulation problems instead of human experts.

Unfortunately, none of existing expert systems in pharmaceutical field supports a generic drug production. In this paper, we purpose the first supporting system using an ontology knowledge base for a generic tablet reformulation. The system provides a suggestion of a certain amount of ingredients and manufacturing process including a set of sequent instructions. The contribution of the purposed system is not only suitable for a tablet reformulation, but also supports a general idea of a drug production in any pharmaceutical dosage form even herbal drug production by simply changing the related knowledge.

The structure of this paper is organized as follows. Section 2 describes a background of previous systems. Section 3 explains the pharmaceutical tablet production ontology and its related production rule. Section 4 defines our system architecture. An evaluation of the system is explained in detail in Sect. 5. Lastly, Sect. 6 concludes the paper and indicates future works.

2. Background

Several supporting systems have been implemented in formulating a pharmaceutical product since 1989. They are categorized into two groups based on knowledge representation, namely production rule based system and frame based system.

2.1 Production Rule Based System

This group of systems represents their pharmaceutical knowledge within production rules. The production rules are conditional statements that specify actions to be taken

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[†]The authors are with the Faculty of Pharmacy, Chiang Mai University, Thailand.
[††]The authors are with Human Language Technology laboratory, NECTEC, Thailand.
a) E-mail: nopphadol@su.ac.th

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or advice if a certain condition is true. There are two types of rules, atomic rules and composite rules. Atomic rule is a simple rule in if-then form. Atomic rules can be integrated together into composite rules, which are a more complex form with multiple conditions and actions. Since there is much knowledge used in a pharmaceutical product development, such as properties of drugs, properties of excipients, incompatibility between ingredients in formulations, and manufacturing processes, production rules become sophisticated. Furthermore, the more rules are defined, the more difficult on handling conflicts among rules will be executed. There are several examples in this group, such as Cadila system and Capsugel system. The Cadila system [4] has been developed to formulate drug tablets based on drug's physical, chemical and biological interrelated properties. The Capsugel system [5] has been implemented to aid the formulation of hard gelatin capsules. It was developed based on a statistical design, information of excipients and a database of marketed formulation. Both systems return outputs in term of ingredient list and their amount. These systems apply rules with information from the database. In fact, they are easy for development, but it cannot handle relations among knowledge in the deep level. In addition, the designed rules are specific for their purposes and they are hardly applied to another application.

2.2 Frame Based System

Unlike the above systems, pharmaceutical knowledge of these systems is particularly separated from production rules and their knowledge is represented in frames. Frame is a structure that represents knowledge in a limited aspect of objects. With the use of frame representation, knowledge in pharmaceutical product development can be represented in a deeper level. Systems in this group include Galenical, Sanofi, Zeneca, and Boots. The Galenical system [6] has been designed to assist the development of a lot of formulations (e.g. aerosols, tablets, capsules, and intravenous injection), using chemical and physical properties of an active ingredient. The output of this system includes 1) formulation 2) production method 3) recommended packaging and 4) prediction of production properties. The Sanofi system [7] has been developed for formulating hard gelatin capsules based on preformulation study (a study on prior knowledge for the active ingredient). The Zeneca system [8] has been designed for formulating tablets, parenterals and film coatings. The Boots [9] system has been implemented to assist the formulation of sun oils, creams and lotions. It is obvious that a frame representation can be applied to several formulation types compared to the first group. Since knowledge represented in frame is restricted to slots which represent concepts in detail, it affects the simpler and clearer production rules.

From those aforementioned systems, their results provide only a list of excipients, their amount, and some attributes of productions such as the capsule size and the tablet diameter. This information alone is not sufficient for inexperienced pharmacists to effectively produce a generic drug since they additionally need production instructions in details in real drug production. Moreover, the systems have been all implemented for the creation of new drugs which have different criteria for drug validation. Therefore, they can scarcely be applied to a generic drug development.

Since the frame representation approach has expressive limits about contiguous relations for deep knowledge, it cannot handle relations among concepts properly. Normally, it is difficult to manage explicit complex relations separated from the frame. For example, an excipient in a drug formulation has a limited range of minimum and maximum concentration based on its function in the formulation. If the concentration of an excipient is lower or greater, the excipient will function in another manner or will possibly become malfunction. These conditions lead to formulation complexity and incomplete formulation issue respectively. Moreover, an incompatibility between two or more compounds is also a limitation of a frame representation. An incompatibility issue becomes much more complicate when two ingredients are mixed and turn incompatible to other ingredients which they are used to be compatible with. In the frame representation, a slot of a frame cannot handle and express these complex conditions sufficiently. In addition, the sequential instructions for tablet production cannot be simply achieved with information in a slot nor a usual relational schema.

Regarding complex deep knowledge in pharmaceutical generic tablet reformulation and production, our framework is designed based on ontology, which is apparently beyond the limitation of a usual relational schema and a frame representation in terms of hierarchical relation and additional complex relation between concepts. Our designed ontology is a knowledge base that completely draws on pharmaceutical domain knowledge of human expert. It also enables us to share and reuse knowledge in the system or across systems effectively.

3. Ontology-Based Knowledge Development

We use ontology to represent knowledge for its explicit specification of a shared conceptualization. To separate between declarative and procedural knowledge, we divide knowledge into two types: the domain knowledge and the operation knowledge. The domain knowledge is a declarative knowledge which is represented in ontology. The operation knowledge is a procedural knowledge which is represented in production rule.

3.1 Design of Domain Knowledge

There are two main knowledge types in the domain knowledge: the general knowledge and the specific knowledge. The general knowledge is knowledge of tablet excipients which explains their properties, possible operation and manufacture suitable for them and drug formulation composition. We design this knowledge following the Handbook

of Pharmaceutical Excipients [10]. The specific knowledge focuses on the original tablet formulation which is generated from literature and patent reviewing. It includes a list of the original tablet ingredients without any property and incompatibility and stability of an active ingredient in the formulation.

3.1.1 The Design of Pharmaceutical Tablet Production Ontology

A pharmaceutical tablet production ontology (PTPO) [11] is created by using an ontology editor called Hozo Environment [12]. The PTPO development process [13] is based on the following steps.

A. Design Classes

In PTPO, a tablet production class represents the definition of drug formulations. It consists of an active ingredient, excipients, formulation processes, a standard quality control (SQC), an equivalent quality control (EQC) and a caution.

The *main drug class* contains data of an active ingredient in tablet formulation. The *excipient class* provides data of other inactive ingredients which play a role in constructing a quality tablet, such as binder, diluent, disintegrant, and so on. The *process class* represents all activities used in manufacturing tablet. The *standard quality control* class is drug-independent quality controls used for validation a tablet quality based on United State Pharmacopeia standard, such as, weight variation, friability and content uniformity. The *equivalent quality control* (EQC) class is drug-dependent quality controls which are applied to validate between the original tablet and the produced generic tablet such as a dissolution profile. Lastly, the *caution class* is a class that represents problems in the experimental process. It reminds the pharmacist who reformulates the new drug alternatives about production process problems, such as binding, sticking and lamination.

B. Design Class Hierarchy

A class hierarchy is designed to identify the organized hierarchical structure among concepts in the tablet production. The relation of class hierarchy shows *is-a* relation to identify a subsumption relation. For example in Fig. 1, the *process class* represents a sequence of unit operations in PTPO. It explains that the manufacturing process is a generalization of a granulation process[†] (G) and a direct compression process[††] (DC). In deeper level, a granulation process can be classified into a wet granulation (WG), and a dry granulation (DG). Another example of a class hierarchy is the *unit operations class*. It represents the fundamental methods using in the tablet production which can be divided into four main methods: mixing, drying, communition, and compression.

C. Design Role Concept

In the tablet formulation, the excipients represent chemical substances which assist on formulating pharmaceutical tablets. One excipient can be functioned in many purposes based on its concentration. In different formulations, a role of the same excipient can vary depending on the purpose. We apply a role-concept *tablet production class* to handle this complexity. Roles are sets of actions that allow for multiple purposes. Basically, the excipients have their own concepts of possible roles. When they are selected in tablet formulation, their role are fixed based on the domain knowledge previously assigned by experts.

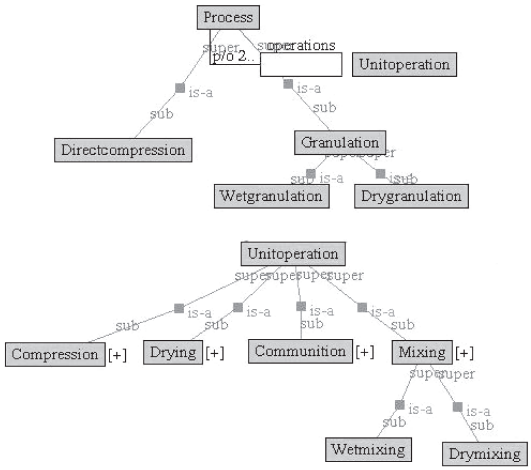

Fig. 1 An example of class hierarchy.

D. Design Additional Relations

Since we aim at defining a strong explicit relation, we solely concentrate on an *is-a* relation, a *part-of* relation and a *role concept*. However, in the tablet formulation, we need a strict order of unit operations to control their sequences. Additional relations are required to explicitly declare a sequence of unit operations. They are designed as additional relation classes, such as *precede relation* class which defines the order of two unit operations. In some cases, two excipients are incompatible between them when formulated together in pharmaceutical tablet. *Incompatiblewith* relation is designed to constrain the related classes in the pharmaceutical tablet formulation. It is defined to support incompatible situations between two excipients. For example, the Millard reaction is the reaction in lactose that affects tablet to change its color and become inactive because of malfunction in a main drug with ammonium functional group. Additional relations are represented in term of relation class which experts can define individually apart from the fundamental relations, such as *is-a* relation or *part-of* relation.

The PTPO currently has six main classes, 126 subclass, five relations and ten role-concepts in total.

[†]A granulation is a process of using a liquid binder or lightly compaction to agglomerate the powder mixture before it is compressed as tablets.

[††]A direct compression is a process that does not require an initial method to compress the powder.

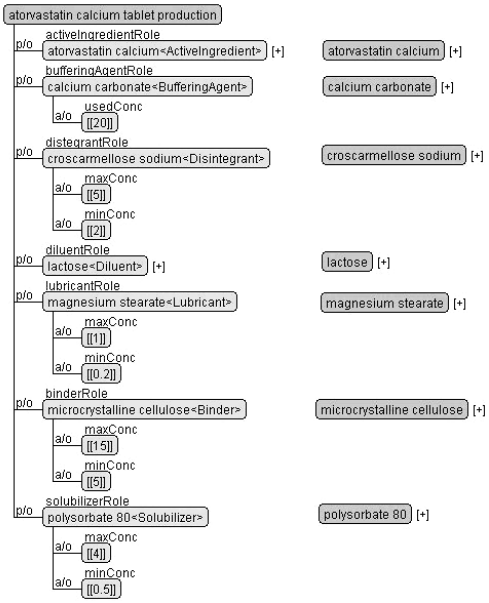

Fig. 2 An example of Atorvastatin Calcium instances.

3.1.2 Instantiation of Pharmaceutical Tablet Ontology

After the ontology is created, the excipients and the tablet productions are instantiated by experts. They are represented in OWL-Lite instead of RDF since an RDF only provides a content data model for representing the basic elements for making simple statements about resources [14] and it is not suitable for complex semantic expression of the PTPO. For example, *is-a*, *part-of*, *precede* relations among classes in PTPO cannot be expressed in RDF. There are two methods for instantiation, mapping from database into ontology instance and instantiating manually using Instance Editor from Hozo environment. The former is suitable for developing formulation which data already exist whereas the latter is appropriate for a new instance creation. An example of the tablet production instances developed in Hozo environment is shown in Fig. 2.

3.2 Design of Operation Knowledge

The operation knowledge is represented as production rules. They are collected from experience of experts and generic tablet formulation experiments. The operation knowledge is designed to formulate the generic name drug tablet based on; (1) an active ingredient's preformulation study such as physiochemical properties and (2) characteristics of an original drug tablet such as disintegration time and dissolution profile. The components of production rules are represented in the following form:

IF ⟨condition(s)⟩ THEN ⟨action⟩.

When the ⟨condition(s)⟩ is triggered, the ⟨action⟩ will be executed. Fifty six production rules are employed in the present version.

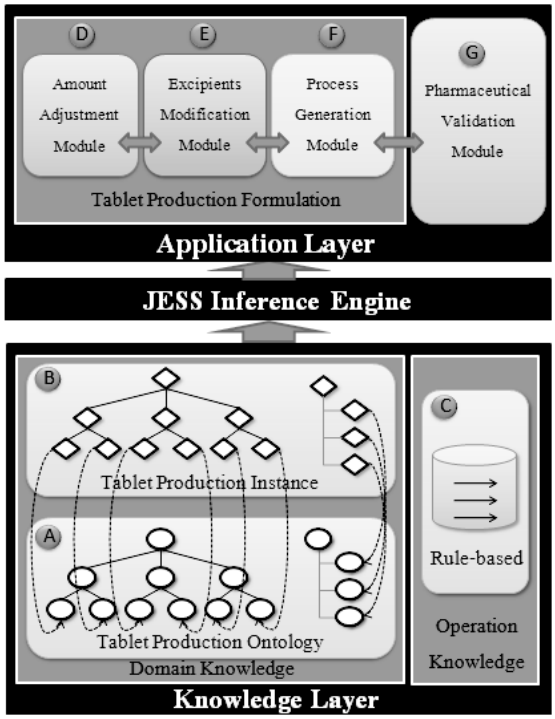

Fig. 3 A framework of the system.

4. System Architecture

As shown in Fig. 3, our framework is designed to assist pharmacists to generate a tablet production of generic drug. The necessary data from PTPO (A), instances (B), and production rules (C) are processed in JESS inference engine [15]. They form the system knowledge base to effectively recommend a solution in our framework. The tablet production system consists of four modules.

1. Amount adjustment module (D)
2. Excipients modification module (E)
3. Process generation module (F)
4. Pharmaceutical validation module (G)

4.1 Amount Adjustment Module

Based on ingredients declared in a patent, the system adjusts the most suitable percentage amount per tablet of each excipient to suggest a generic drug production. An appropriate amount of the excipients are calculated based on their function in tablet formulation. The dissolution profile and integration time are also applied in rules if they are inputted into the system. The appropriate amount has to be set within the range between minimum and maximum value.

4.2 Excipients Modification Module

Normally, a patent gives us the information of main drug and all excipients. The formulation provided by the system will not modify excipients but only specify amount of them.

However, since there are various types of each excipient, it is possible to apply different types when comparing to the information from a patent. The objective of this module is to modify excipients if the given ingredients cannot reformulate the appropriate tablet production of generic drug because of limitation of excipient amount range. Modifying excipients is a strategy to be applied together with the *amount adjustment module*, and propose a new generic drug formulation. Modifying strategies are adding and substitution depending on role of the focusing excipient. Whenever the new ingredients are determined, amounts of all excipients have to be re-calculated in amount by the *adjustment module*.

4.3 Process Generation Module

This module is designed to generate a set of production instructions from the given excipients and their amount value. The process is determined from physicochemical properties of drug and characteristics of tablet.

4.4 Pharmaceutical Validation Module

This module is designed to evaluate the pharmaceutical equivalence between the standard quality of original drug and the experimental quality result of the inputted generic drug. Difference (f_1) and Similarity (f_2) factors are determined by performing the requisite dissolution rate testing on twelve tablets according to the FDA's Guidance on Dissolution Testing of Immediate Release Solid Oral Dosage Form [16]. The difference factor (f_1) is a measurement of the relative error between the generic drug formulation curve and the trade name drug formulation curve whereas the similarity factor (f_2) is the measurement of dissolution curve between the generic drug and the trade name drug. If the f_1 values range between 0 and 15 and f_2 values range between 50 and 100, both dissolution curves are compared. The range of similarity of f_1 and f_2 is set up between 0 and 100. The validated generic drug tablet is satisfactory unless the curve reaches over the acceptable range. These factors can be determined using the following equations [16]:

$$f_1 = \left\{ \frac{\left[\sum |R_t - T_t|\right]}{\left[\sum R_t\right]} 100 \right\} \tag{1}$$

$$f_2 = 50 \log \left\{ \left[1 + \frac{1}{n} \sum w_t (R_t - T_t)^2 \right]^{-0.5} 100 \right\} \tag{2}$$

Where: f is a fit factor; Rt is a reference assay at time t (percent dissolved); Tt is a test assay at time t (percent dissolved); n is a number of sample points; wt is a weight at time t (optional); S is a summation of t from 1 to n.

5. Evaluation

To evaluate the system, four original drugs are randomly selected as representative samples based on the active ingredient (API) criteria. The first criterion is a solubility of API.

Table 1 Four sample tablets for evaluation.

		Dose and ratio of active ingredient	
		B1	**B2**
Solubility of active ingredient	**A1**	Metformin Hydrochloride	Hydroxyzine Hydrochloride
	A2	Paracetamol	Atorvastatin Calcium

Solubility can be categorized into two groups. *A1* refers to a group of a tablet that contains very soluble, freely soluble or soluble API whereas *A2* denotes to a group of a tablet that contains sparing soluble, slightly soluble, very slightly soluble or practically insoluble API. The second criterion is a dose and ratio of API. A percentage amount of an active ingredient is classified into two types. *B1* indicates a group of a tablet that its API is lower than 25% from the total dose whereas *B2* designates a tablet that its API is over 25% from the total dose. These two factors are focused to certainly cover all different issues of generic tablet production. The four representatives are shown in Table 1.

Based on the validation criteria mentioned in Sect. 4.4, the generic products of metformin hydrochloride, paracetamol and hydroxyzine hydrochloride produced regarding the system suggestion are all acceptable from the first suggestion. For the generic products of atorvastatin calcium, they are not pharmaceutically equivalent for the first trial. The system; therefore, executed the *excipients modification module* and gave the pharmaceutically equivalent formulation and production in the later attempt. To explain a process and related knowledge used in the system, the case of the atorvastatin calcium is exemplified in detail since all modules of the system was applied before the suggestions were satisfactory. In the system, a work flow process are separated into four processes, 1) preliminary process, 2) generic drug tablet reformulation process, 3) laboratorial production process, and 4) pharmaceutical equivalence validation process.

A preliminary process is a process for users to gather information from both a preformulation experiment of an original drug in laboratory and a patent reviewing. From a preformulation process in a laboratory, users acquire characteristics[†] of original drug tablet and properties of an active ingredient (API) such as flowability and compressibility. From an original drug patent reviewing, user gains a list of excipients, the active ingredient with its amount, and its properties such as solubility and stability [17]. In a preliminary process, the obtained information of the Atorvastatin Calcium and its active ingredient (API) is illustrated in Table 2.

A generic drug tablet reformulation is a process to generate a generic formulation based on the input from preliminary process. In this process, the system returns a generic

[†]The characteristics of a tablet are a disintegration time of a tablet, a dissolution profile of a tablet, tablet hardness, a fragment surface, etc.

Table 2 The Atorvastatin Calcium information.

Information type	Value
Solubility	Very slight soluble
Flowability	Fair
Fracture surface	Rough
Temperature stability	Stable
Moisture stability	Stable
API weight	20 mg.
Tablet weight	300 mg.
Hardness	5.2 kg.
Disintegration Time	50 sec.
Dissolution profile (%) at a minute of 5/10/15/30/45/60	91.08/98.37/101.04/101.07/101.28/101.20
Ingredients [known amount]	• Atorvastatin calcium [20 mg.] • Calcium carbonate • Croscarmellose sodium • Microcrystalline cellulose • Lactose • Magnesium stearate • Polysorbate 80

Table 3 The suggestion for the generic atorvastatin calcium.

List of ingredients	Function	Weight
Atorvastatin calcium	Active ingredient	20.00 mg.
Calcium carbonate	Buffering agent	60.00 mg.
Croscarmellose sodium	Disintegrant	15.00 mg.
Microcrystalline cellulose	Binder	45.00 mg.
Magnesium stearate	Lubricant	0.60 mg.
Polysorbate 80	Solubilizer	12.00 mg.
Lactose	Diluent	147.40 mg.
Other suggestion	**Value**	
Manufacturing process	Wet granulation	
Instructions in order	1. Wet mixing API and solubilizer 2. Dry mixing the mixture from 1 with disinitegrant, binder, buffering agent and diluent. 3. Wet mixing the mixture from 2 with water until it wet. 4. Communition with sieve no.14 5. Drying 6. Communition with sieve no.18 7. Compression	

drug production which includes all ingredients with their amount, manufacturing process and a set of instructions. For the atorvastatin calcium, the system generated the suggestion shown in Table 3.

The system sets up amount values of excipients at *amount adjustment module*. An amount of each ingredient is calculated from the given tablet characteristics and the properties of main drug. The calculation and adjustment are based on *operation knowledge*. An available amount range of each ingredient is informed in *domain knowledge*.

Table 4 The rules used in the suggestion of the atorvastatin calcium.

Rule no.	Detail of rule
I	IF <buffering agent exists> THEN <set the concentration of buffering agent at normal concentration>
II	IF <disintegration time of the original is less than or equal 180 seconds> AND <type of disintegrant is super-disintegrant> THEN <set the concentration of disintegrant at maximum concentration>
III	IF <hardness of the original is more than 5 kg> AND <type of binder is hardest> THEN <set the concentration of binders at maximum concentration>
IV	IF <solubility of API is sparing soluble or slightly soluble or very slightly soluble or practically insoluble > THEN <set the concentration of lubricant at minimum concentration>
V	IF <solubility of API is sparing soluble, slightly soluble, very slightly soluble, or practically insoluble> THEN <set the concentration of solubilizer at maximum>
VI	IF <diluent exists> THEN <set diluent with the left amount>
VII	IF < API concentration is less than 10%> THEN < set the process type as Wet granulation >

From the atorvastatin calcium case, the *operation knowledge* represented in the rules given in Table 4 was applied according to *domain knowledge* shown in Fig. 2. For example, the microcrystalline cellulose which plays a binder role is set to maximum regarding the rule III. In addition, the manufacturing process of the atorvastatin calcium is set to a wet granulation because the condition of rule VII was triggered.

The formulation result is consequently transferred to *process generation module* to generate a set of instructions based on those values [18].

After the system returns a result, generic tablets were produced based on the suggestion in the laboratorial production process by pharmacists. The produced tablets were tested in quality controls by user in laboratory. The quality control results were filled in the system to calculate f_1 and f_2 score to validate its quality in a pharmaceutical equivalence validation process. Once the result of the produced drug is validated that it contains a pharmaceutical equivalence, the system process is terminated. For the atorvastatin calcium case, the quality control results of the generic based on the suggestion given in Table 3 are shown in Table 5.

Since the result in Table 5 is unacceptable, the details from quality control and dissolution are utilized as additional information for an improvement of a later suggestion. To improve a suggestion, differences of an average

Table 5 The pharmaceutical equivalence result between the original and the generic atorvastatin calcium following system suggestion.

Dissolution profile (%) at a minute of 5/10/15/30/45/60/average		Disintegration Time (sec.)	
Original	**Generic**	**Original**	**Generic**
91.08	54.05	50	193
98.37	61.75	**Pharmaceutical Equivalence**	
101.04	64.25		
101.07	65.22	**F_1**	**F_2**
101.28	65.50	36.51	23.75
101.20	66.38	**> (0-15) Fail**	**< (50-100) Fail**
99.01	**62.86**		

Table 6 The improvement rules used in the atorvastatin calcium.

Rule no.	Detail of rule
I	IF <dissolution profile is over an acceptable range> AND <solubilizer is at maximun> AND <wetting agent does not exist> THEN <add wetting agent excipient with a half amount of existing solubilizer and decrease the amount of the existing solubizer to half>
II	IF <disintegration is over an acceptable range > AND <disintegrant is at maximun> AND <type of disintegrant is super-disintegrant> AND <another excipient has a possible role as disintegrant> THEN <set a concentration of the excipient that has a possible role as disintegrant to perform a role of disintegrant function>

dissolution profiles and disintegration time between original and generic products are focused. Both of the values of the generic product are not allowed to be below or over 10% of the original product.

In the example case, the average of dissolution profile of the generic version is over 10%. Moreover, the disintegration time of generic product also needs improvement since it also exceeds 10% of the disintegration time of the original product. To improve a suggestion, the rule I and II in Table 6 are triggered to add a wetting agent to the formulation and to adjust a concentration of the binder, respectively. After the excipients and amounts were modified, the set of instruction were rebuilt accordingly. The modified suggestion of the atorvastatin calcium is shown in Table 7. The generic products were later produced following the given improved suggestion and they finally showed a pharmaceutical equivalence result. Table 8 illustrates the pharmaceutical equivalence result between the original and the improved generic atorvastatin calcium. Hence, the process was satisfactorily completed.

6. Conclusion and Future Work

In this paper, we propose a framework of a pharmaceutical supporting system for generic tablet reformulation and production. An ontology is exploited to represent domain knowledge of excipients and tablet formulation from document, literature and patent reviews. Beside, production rules represent operation knowledge from experience of experts and generic drug tablet formulation experiments. The number of classes, relations, role-concepts and rules in the present version are one hundred twenty six, five, ten and fifty six, respectively. The system consists of four modules which are the amount adjustment module, the excipient modification module, the process generation module and the pharmaceutical validation module. The first three modules assist a user in generating a generic drug production. The pharmaceutical validation module facilitates the user to validate a pharmaceutical equivalence between the

Table 7 The improved suggestion for the generic atorvastatin calcium.

List of ingredients	Function	Weight
Atorvastatin calcium	Active ingredient	20.00 mg.
Calcium carbonate	Buffering agent	60.00 mg.
Croscarmellose sodium	Disintegrant	15.00 mg.
Microcrystalline cellulose	Binder	**75.00 mg.**
Magnesium stearate	Lubricant	0.60 mg.
Polysorbate 80	Solubilizer	**6.00 mg.**
Sodium lauryl sulfate	**Wetting agent**	**6.00 mg.**
Lactose	Diluent	147.40 mg.
Other suggestion	**Value**	
Manufacturing process	Wet granulation	
Instructions in order	1. Wet mixing API and solubilizer 2. Dry mixing the mixture from 1 with disinitegrant, binder, buffering agent and diluent. 3. Wet mixing the mixture from 2 with water until it wet. 4. Communition with sieve no.14 5. Drying 6. Communition with sieve no.18 **7. Dry mixing mixture and magnesium stearate** 8. Compression	

Table 8 The pharmaceutical equivalence result between the original products and the improved generic atorvastatin calcium.

Dissolution profile (%) at a minute of 5/10/15/30/45/60/average		Disintegration Time (sec.)	
Original	**Generic**	**Original**	**Generic**
91.08	89.81	50	46
98.37	100.86	**Pharmaceutical Equivalence**	
101.04	102.91		
101.07	102.86	**F_1**	**F_2**
101.28	103.06	1.93	84.29
101.20	103.45	**= (0-15) Acceptable**	**= (50-100) Acceptable**
99.01	100.49		

generic products following the suggestion of the system and the original products.

Based on the evaluation result, the system shows promising potential in term of successful reformulation of four random sampling original. Especially, three of them showed the pharmaceutical equivalence to their original products from the first recommendation.

In the future, we plan to develop a user-friendly interface for users to directly instantiate their excipient information and condition rule into the knowledge base. Moreover, we plan to improve the system for supporting an herbal tablet production which is a traditional product in a pharmaceutical market of several countries. Lastly, we also plan to adapt our system and ontology to other dosage forms such as capsule, liquid and powder.

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Nopphadol Chalortham received the B.S. in Pharmacy and M.S. Degrees in Management and information Technology from Chiang Mai University in 1996 and 2004, respectively. He is a Ph.D. student at Chiang Mai University since 2005. He is now with the Faculty of Pharmacy, Silpakorn University in Thailand.

Phuriwat Leesawat received the M.S. degree in Industrial pharmacy from Chulalongkorn University in 1991. He also received the Ph.D. degree in Industrial and Physical Pharmacy from the Purdue University, USA. in 1999, respectively. During 1999-present, he has been with pharmaceutical science department, Pharmacy faculty, Chiangmai University in Thailand.

Taneth Ruangrajitpakorn received the B.A. Degree from College of Religious Study, Mahidol University in 2000. He received the M.A. in Computational Linguistics from Chulalongkorn University in 2005. Since 2003, he has been with the Human Language Technology laboratory at National Electronic and Computer Technology Center in Thailand.

Thepchai Supnithi received the B.S. Degree in Mathematics from Chulalongkorn University in 1992. He received the M.S. and Ph.D. degrees in Computer Engineering from the Osaka University in 1997 and 2001, respectively. Since 2001, he has been with the Human Language Technology Lab at National Electronic and Computer Technology Center in Thailand.