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CASE STUDY AND REPORT

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An Ontological Informatics on Development of Tablet Drug in Pharmaceutical Industry

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Abstract:In production enterprise like pharmaceutical, considerable time and money is spent in training new employee to be familiar with fundamental process of production and to master its complexity. Since the training does not guarantee trainees' good understanding, the complex structure of production is retained. There is need for Pharmaceutical students to be familiar with industry based realities concerning production process. Therefore, a knowledge based system is needful to aid industrial training process and teaching, The knowledge based system, in this case, which is an ontology, will enable trainees and students to systematically learn at their pace in order to master the complexity of the production process. Thus, this paper develops a task oriented ontology which is explicit, expressive, and can naturally represent the production activities of tablet drugs. The ontology is built by formalizing the terminologies and constraints based on both Allen interval temporal logic and McDermott's logic of time points. The axioms were written in first order logic and implemented using Prolog programming language. The competency of the ontology was tested using competency questions, which the ontology could answer, with the use of simple queries. The ontology developed can be reused in representing production activities of capsules, gels, injections and creams.

Keywords:knowledge based system; tablet drugs; formalization; production process; ontology.

I. INTRODUCTION

Knowledge this day is more relevant to sustain business than capital, labour or land, yet it is not readily available. Knowledge thus is the most important competitive resource of any enterprise [1]. Ontological development is one of the ways of making knowledge readily available in industry. An ontology is the conceptualization of domain knowledge i.e. description of concepts and relationships that exists among agents in a domain [2][3] [4]. Ontology can be rule-based and this work uses a rule-based approach because of its intention to expressively and naturally represent knowledge that are involved in the production process [5]. The resulting rule-based ontology is built into a knowledge base. A knowledge base explicitly stores knowledge about a particular domain, and uses inference engine to arrive at conclusion on query about knowledge which is not explicitly stated. Ability to infer through inference engine is what makes a knowledge base different from a database.

Knowledge based system has been applied to various aspects in manufacturing industries. Examples of such applications are: for maintaining competitiveness, product formulations for both new and upgrade products [5][6], innovations [7][8], detection of anomalies or exceptions, planning and scheduling [9] and product development quality control [10] among others. Based on literatures found and reviewed, it is scarce to find work on development of knowledge based that can aid training process in pharmaceutical industry or to aid teaching-learning process of pharmaceutical students. As an aid to training process, this knowledge base will reduce cost and time spent in training and re-training new industrialist. It will also aid the new industrialist to quickly comprehend the complex structure of production process. In addition, it will reduce chances of making costly mistake because the knowledge base will always be available to be queried even though experts may not always be readily available. In addition, this work bridged practical knowledge-gap between industrial experts and the academician by using knowledge-base to bring industry realities into the

II. KNOWLEDGE ENGINEERING PROCESS

The knowledge engineering process gives the general view of the methodology used in building this ontology. Figure 1 shows the various stages of knowledge engineering with their respective deliverables as follows:

- knowledge acquisition, which has hierarchy of production activities and competency questions as deliverable,
- formalization , which has axioms as deliverables, and
- implementation of axioms using Prolog.

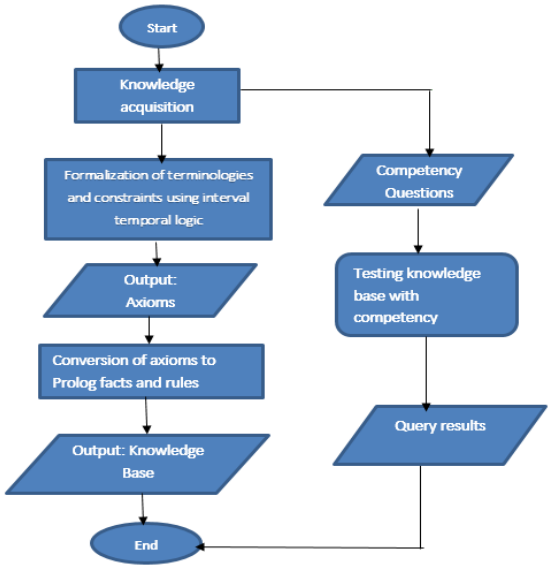

Figure 1. Flowchart showing knowledge engineering process

III. KNOWLEDGE ACQUISITION

Knowledge acquisition is about finding facts and details about the production activities of tablet drug in a Pharmaceutical Industry domain. This helps to identify domain terminologies such as concepts/objects, attributes/properties of objects, and the relations among objects in the domain.

Domain terminologies and their relationships are used to design the structure of production activities of tablet drugs. There are eleven stages in the production of tablet drug; each stage in the ontology is referred to as a concept/class. In the hierarchy, each class has sub-classes and each sub-class has attributes or properties, which are constrained by time and sometimes by size. Section IV discusses the structure of the production activities.

IV. STRUCTURE OF PRODUCTION ACTIVITIES

There are eleven stages involved in the production activities of tablet drug. These are Paste preparation, RMG mixing, Wet milling, Drying, Sieving, Dry milling, Blending, Compression, Blistering, Packaging and Storage.

A. Paste Preparations

Paste preparation of chemicals that require water is done through the following steps:

- Determine the quantity of water by considering the nature of the chemical and the production the paste will be used for.
- Prepare two containers, one for cold mixing of the chemical, the other one for the actual paste preparation.
- Cold mixture of the chemical is done in one container and the other container is used to boil water up to 100 degree centigrade.
- When the water boils, the cold mixture is poured into the boiling water and it is stirred with the boiling water until a translucent paste is formed.

Figure 2 shows the hierarchy of Production activities at the first stage- Paste preparation. It shows how paste preparation translates from coldmixing activity into translucent paste.

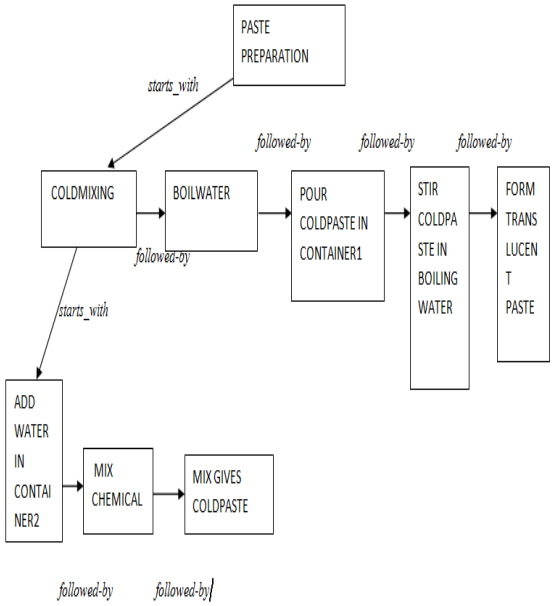

Figure 2. Structure showing formation of translucent paste

B. RMG Mixing

RMG mixing follows these steps:

- Dry chemical is charged into RMG machine (this machine is a mixer).
- The RMG timer is set, the RMG lid is covered and the machine is switched on, the timer causes the RMG to stop automatically.
- The RMG lid is opened and translucent paste is charged into the RMG.
- The RMG lid is left opened and the RMG is switched on again.
- The mixing process is observed until wet mass is formed.
- When the wet mass is formed the speed of the RMG is reduced and the wet mass is discharged into a big bowl.

C. Wet Milling

Wet milling of wet mass in the Multimill machine follows these steps:

- Screen of required granule size is inserted into the multimill machine.
- Wet mass is charged into the multimill and the machine is switched on.
- Grinding of wet mass begins until it forms granules of required size (this is known through observation and the granule size is achieved through the screen).The fluid bed drier (FBD) bowl is pushed under the multimill machine. The machine is stopped and the granules are discharged into the fbd bowl.

D. Drying

- Drying of the granule is done to reduce the moisture content of the granule. The steps are:
- The FBD bowl is put on the pneumatic air.
- The time is set based on the required moisture content.
- Machine is switched on.

- The machine is switched off after working for the specified time.
- The analyzer is used to check moisture content of dried granule sample.

E. Sieving

The dried granule is sieved to separate fine granules from coarse granule by following these steps:

- Insert sieve mesh into the sifter. The size of the sieve mesh is based on the size of the required granule.
- The dried granule is charge into the sieve mesh and the agitator is switched on.
- As the agitator vibrates fine granules is separated from coarse granule.

F. Dry Milling

Dry milling is done so that the coarse granule from the sieving process may be grinded into fine granule. Dry milling is done by Multimill machine used for milling dried granule. The following steps are carried out:

- Insert screen of the required size into the multimill machine.
- Charge the coarse-granule into the machine.
- The multmillis switched on and grinding of the coarse granule begins.
- Observation of the grinding process is done with the eyes. This helps to know when the fine granule is formed.
- When the size has been achieved, then the material is discharged into a container.
- The multimillis switched off after discharge of fine granule.

G. Blending

Blending is the process of mixing the fine granules and other required chemical together. It is done through the following steps:

- Charge the fine granule and other chemical into the double cone blender.
- The lid of double con blender is closed.
- The time is set using wristwatch and the machine is switched on.
- The machine is stopped after the set time is completed.
- Blending resulted in fine drug chemical and it is discharged into a tarred container.

H. Compression

Compression is the stage where the compressor is used to produce tablet from fine drug chemical. It follows the following process:

- Set the dice_pore, the upper and lower punch into the compressor.
- Connect the hose of the duster machine with the compressor.
- Load the hopper of the machine with fine drug chemical.
- Switch on the machine. The feeder will take fine drug chemical from hopper into the dice_pore.
- While the fine drug chemical is still in the dice_pore, the upper and lower punch will compress or punch it into tablet form.
- The tablet is discharged into a tarred container and at the same time the duster sucks chemical particles from the dice_pore. This is done to prevent chemical particles from been discharged with the tablet.

I. Blistering

Blistering process is a process of packing the tablets into sachet. Machine used for this is called blistering machine. The following steps are taken:

- Mount the appropriate roller. Choice of roller depends on the shape of the tablet.
- Polyvinyl chloride (pvc) is set on roller. The roller is used to form appropriate shape on the machine.
- The aluminum foil is loaded on the machine. The hopper is loaded with tablets and the machine is switched on.
- The vibrator releases tablet from the hopper to the feeder. The roller forms the appropriate pvc shape.
- Tablet from feeder drops into shaped pvc. An operator will be there to take excess tablet.
- The sealed pvc is rolled under the sealing heater where it is sealed with aluminum foil.
- The sealed pvc is knurled and cut by the cutter to make sachets.

J. Packaging

Packaging is done to make sachets into packets and packets into carton. The process is as follows:

- Production date and expiry date are embossed on each sachet, packet and shipper box (carton).
- A number of sachets are packed into an empty packet. A number of packets are wrapped with nylon and a hot iron is used to shrink the nylon. A number of wrapped packets are packed into a shipper box.

K. Storage

Shipper box is kept in stores until the sales department makes request for it.

V. FORMALIZATION OF THE CONCEPTS

Formalization is done to produce formal specifications of all the events, attributes of events, and constraints on events that occur during production activities of tablet drugs. The Formalization is done using Allen interval temporal logic and McDermott's logic of time points. Allen interval temporal logic is used in order for the knowledge base to naturally reflect how production activities is carried out with respect to time. Allen is combined with McDermott's logic of time points so that events that occurred at instant may be naturally represented in the knowledge base. Equations 1,2, and 3 are axioms or knowledge representation of the first stage of the production activities.

$$\forall e, t.\, coldmixing(e, t)$$
$$\Leftrightarrow \exists con2, chemical, water.\, \exists e1.\, add(e1, water, con2, t1)$$
$$\wedge \exists e2.\, mix(e2, con2, t2) \wedge meets(t1, t2) \wedge \exists e3.\, mix$$
$$- gives(e3, coldpaste, t3) \wedge overlap(t2, t3) \wedge ends(t3, t).$$

(1)

Axiom 1 simply says that for all event e at time t, where e is coldmixingoccurs if and only if there is water, container2, chemical, and coldpaste. Such that there exist events add water e1, mix e2,and mix_gives e3, that occur concurrently at time t1, t2, and t3 in such a way that the time of event add meets the time of event mix and event mix and mix_gives overlap, while event mix_gives end the event coldmixing.

$$\forall e, t.\, boilwater(e, t)$$
$$\Leftrightarrow \exists water(w), container1(c1).\, \exists e1.\, pour$$
$$- in(w, c1, t1) \wedge \exists e2.\, heat - till - boil(w, c1, t2)$$
$$\wedge meets(t1, t2) \wedge ends(t2, t).$$

(2)

Axiom 2 says that for all event e attime t where event is boilwater. The boilwater that spans through time t occurs if and only if, there exists water, and container1, such that there exist event pour_in e1, of water in container1 at time t1 and event heat_to_boil e2, in container1 at time t2 and time t1 meets time t2 and time t2 ends t.

$$\forall e, t.\, paste - preparation(e, t)$$
$$\Leftrightarrow \exists coldpaste(cp), container1(c1), container2(c2).\, \exists e1(e1, ch, c2, cp, t1)$$
$$\wedge \exists e2.\, boilwater(e2, c1, t2) \wedge meets(t1, t2)$$
$$\wedge \exists e3.\, pour(e3, cp, c2, t3) \wedge \exists e4.\, stir(e4, cp, c1, t4) \wedge overlap(t3, t4)$$
$$\wedge \exists e5.\, form(e5, tp, t5) \wedge ends(t5, t).$$

(3)

From axiom 3, every paste_preparation event that spans through time t occurs if and only if there exists coldpaste, container1, and container2, such that there exists event coldmixing e1, of chemical in container2 to give coldpaste at time t1 and event boilwater e2, in container1 at time t2 and time t1 meets time t2 and event pour coldpaste from container2 at time t3 and event stir coldpaste in container1 at time t4 and time t3 overlaps time t4 and event form translucent paste at time t5 and time t5 ends time t.
Other stages are also formalized using the same logic.

Competency questions are common sense questions that the knowledge base should be able to answer in order to prove its competency. The competency question is developed from interactions with the industrial expertise on how they perform the task of production activities of tablet drugs and the challenges they are facing in doingthis. They were developed in order to facilitate training such that the trainee will easily understand the complex structure involved in production of tablets drugs. Some of the competency questions are:

- What are the end products of each stage?
- What are those things needed in a particular activity?
- What is the duration involved at each stage?
- What are the activities involved in a particular stage?
- What are the important parameters that a stage cannot do without?
- How do we plan for a given activity in the future?

VI. IMPLEMENTATION AND RESULT

All the first order logic axioms were implemented in Prolog programming language and the competency of the ontology was tested with the competency questions. Figures 4 – 8 show the screen shots of some of the results.
Figure 4 shows the listings of all production activities which answers the competency questions ‘what are the general stages involved in production process’?

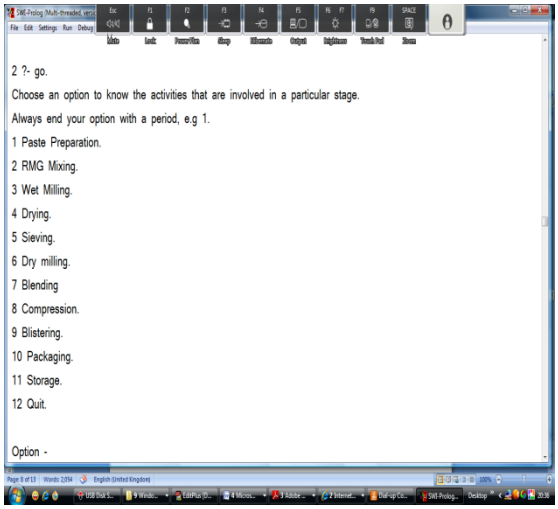

Figure 4. Screen shot of all the stages of production

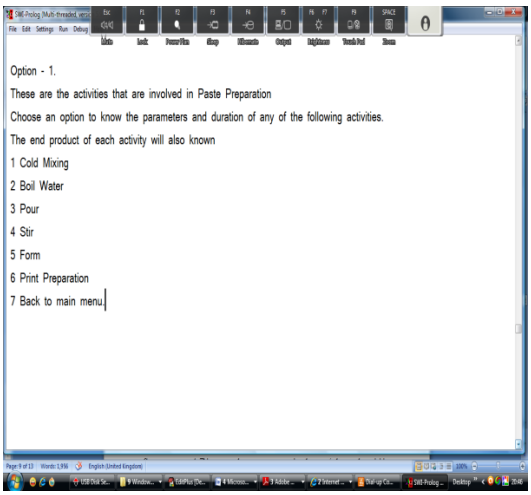

Figure 5: Screen shot showing all the activities of Paste preparation

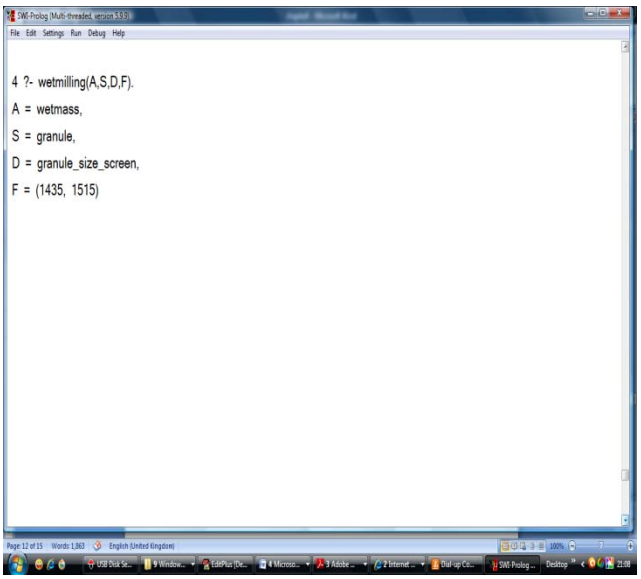

Figure 6. Screen shot result-showing parameters in Wetmilling activity

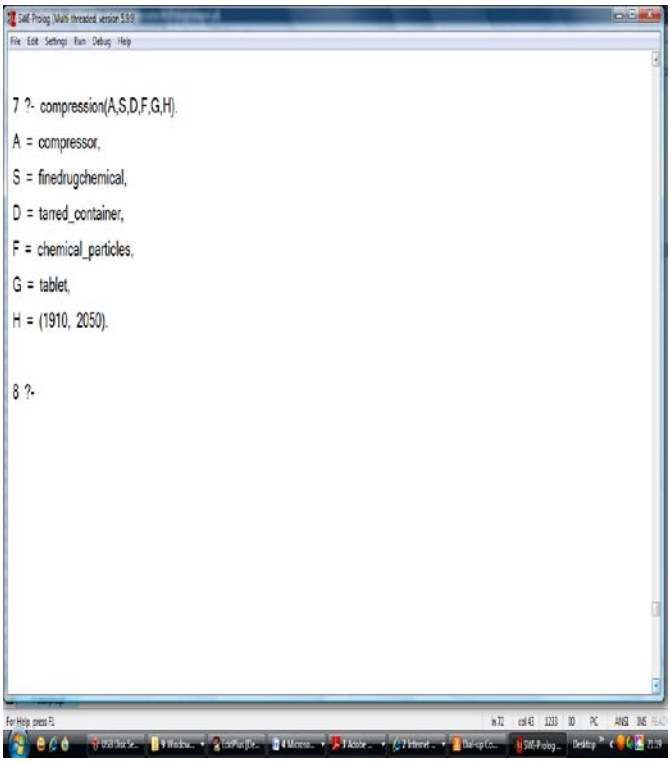

Figure 7. Screen shot result of Parameters in Compression Activity

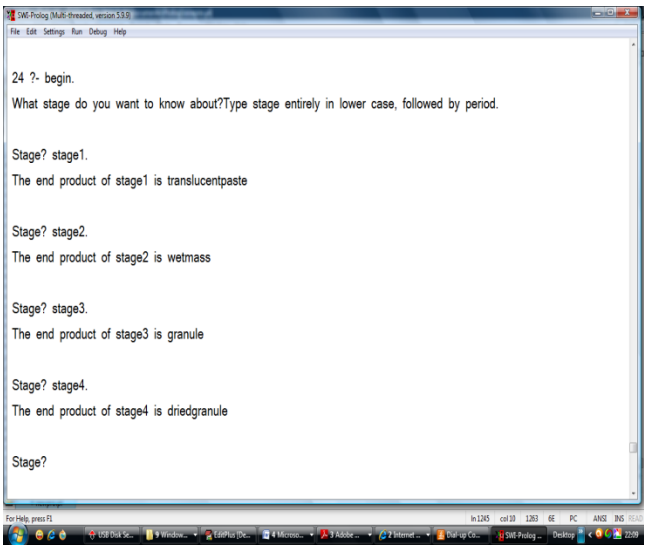

Figure 8. Screen Shot Result Showing End product of Specific Stage

VII. CONCLUSION AND FUTURE

Thus from the results it has been shown that the ontological model knowledge base is competent according to the competency question. The highly expressible power of Prolog and interval temporal logic in representing continuous change realistically has made this to be possible.

We aim to capture in knowledge base problems or challenges facing different stages of production process and provides previous solutions rendered by experts. This will preserve expert knowledge and serves as a bridge between the industry and the academics.

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