CHAPTER 4

RESULTS AND DISCUSSION

4.1 Evaluation result of generic drug tablet production from OXPIRT

Based on section 3.4.1, four representatives of two factors are tested separately. There are 1) metformin hydrochloride, 2) paracetamol, 3) hydroxyzine hydrochloride, and 4) atorvastatin calcium. Each of them is trialed following the method in Section 3.4.1.2. Below, a result of each representative including discussion is presented.

4.1.1 Metformin hydrochloride tablet production

From preformulation study, information of metformin hydrochloride powder (API) and the original tablet of metformin hydrochloride (Glucophage®) are obtained. Information of API is given in Table 4.1and information of the original tablet is shown in Table 4.2.

Table 4.1 The information of metformin hydrochloride powder (API)

Solubility	Flowability	Stability	
		Temperature	Moisture
Freely soluble	Poor	Stable	Stable

Table 4.2 The information of Glucophage® tablet (Product)

Information of Glucophage® tablet	Value
Fracture surface	Rough
API weight (mg.)	500
Tablet weight (mg.)	530
Hardness (kg.)	9
Disintegration Time (Sec.)	336
Dissolution profile (%) at time 5/10/15/30/45/60 minute	53.51/56.92/61.10/85.06/85.59/89.60

With the information given in Table 4.1 and Table 4.2, OXPIRT system searched through the knowledge and returned a list of ingredients and their function represented in ontology instance which are sketched in Figure 4.1.

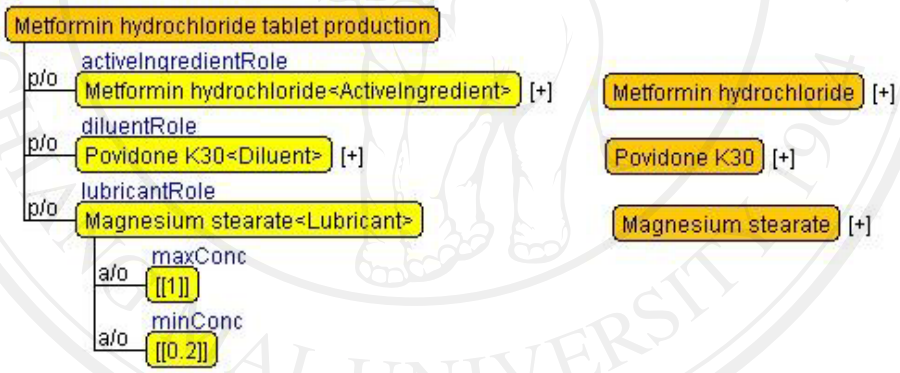

Figure 4.1 The ontology instance of metformin hydrochloride tablet

The system then applied rules for finding appropriate process. The rule used in this situation is shown in Figure 4.2. For literary, since the flowability of this API is poor and fracture surface is rough with stable temperature and moisture stability, OXPIRT chooses a wet granulation process for production of metformin hydrochloride.

IF <flowability of API is poor or very poor or extremely poor>
AND <fracture surface is rough>
AND <temperature stability is stable>
AND <moisture stability is stable>
AND <API concentration is more than 10%>
THEN < set the process type as Wet granulation >

Figure 4.2 A rule for inference of process type as wet granulation

After process type was set, OXPIRT inferred a concentration of unknown amount ingredients and later performed a weight calculation based on the assigned concentration and tablet weight. In this case, two ingredients which are magnesium stearate and povidone K30 were concerned. First, magnesium stearate was involved in the following rule shown in Figure 4.3. With the rule, a concentration of magnesium stearate was inferred to maximum as 1 % and it was computed to weight 5.3 mg.

IF <solubility of API is very soluble or freely soluble or soluble>
THEN <set the concentration of lubricant at maximum concentration>

Figure 4.3 The rule to infer lubricant concentration of very soluble, freely soluble and soluble API

Then, the diluent amount is computed by the total weight minus the available left space from the already set ingredients (i.e., 530 - (500 + 5.3) = 24.7 mg).Finally, a set of instruction was generated based on rules in Figure 4.4 regarding to the assigned information and previously recommended values.

IF <solubilizer does not exist in formulation >
AND <process type is the wet granulation>
THEN <perform dry-mixing unit operation between API and other excipients except lubricant >
THEN < perform wet-mixing unit operation of the dry-mixed mixture with water >
THEN < perform drying unit operation>
THEN < perform resizing unit operation with sieve no. 20>
THEN <perform dry-mixing unit operation of resized mixture with lubricants >
THEN <perform compression unit operation to dry-mixed mixture for at least 5 kg or near hardness of the original tablet>

Figure 4.4 The rule to infer instructions of wet granulation process for no existing solubilizer in formulation

With the all above data, OXPIRT concluded the formulation and production of metformin hydrochloride tablet as shown in Table 4.3.

Table 4.3 The tablet production of metformin hydrochloride

	Function	List of excipient	Weight(mg.)
Tablet Formulation	Active ingredient	Metformin hydrochloride	500
	Binder and Diluent	Povidone K30	28.94
	Lubricant	Magnesium Stearate	1.06
Manufacturing Instruction	Process type	Wet granulation	
	Instructions	1. Dry mixing metformin hydrochloride, povidone K30 2. Wet mixing mixture with water until it wet 3. Communition with sieve no.14 4. Drying 5. Communition with sieve no.18 6. Dry mixing mixture and magnesium stearate 7. Compression	

With formulation and instruction in Table 4.3, the metformin hydrochloride tablet is produced. The tablet is then tested for hardness, disintegration time and

dissolution profile. Table 4.4 shows the three mentioned test results of the produced tablet.

Table 4.4 The hardness, disintegration time and dissolution profile of Glucophage® tablet and metformin hydrochloride tablet

		Glucophage® tablet	**Metformin hydrochloride Tablet**
Hardness (kg.)		9	5
Disintegration time (sec.)		336	326
Dissolution Profile (%) At time (minute)	5	53.51	42.75
	10	56.92	58.69
	15	61.10	69.37
	30	85.06	91.72
	45	85.59	92.62
	60	89.63	90.79

Figure 4.5 shows a comparison of dissolution profiles between the metformin hydrochloride tablet and the original drug tablet (Glucophage®). Table 4.5 shows a pharmaceutical equivalence result by examining difference factor (F_1) and similarity factor (F_2).

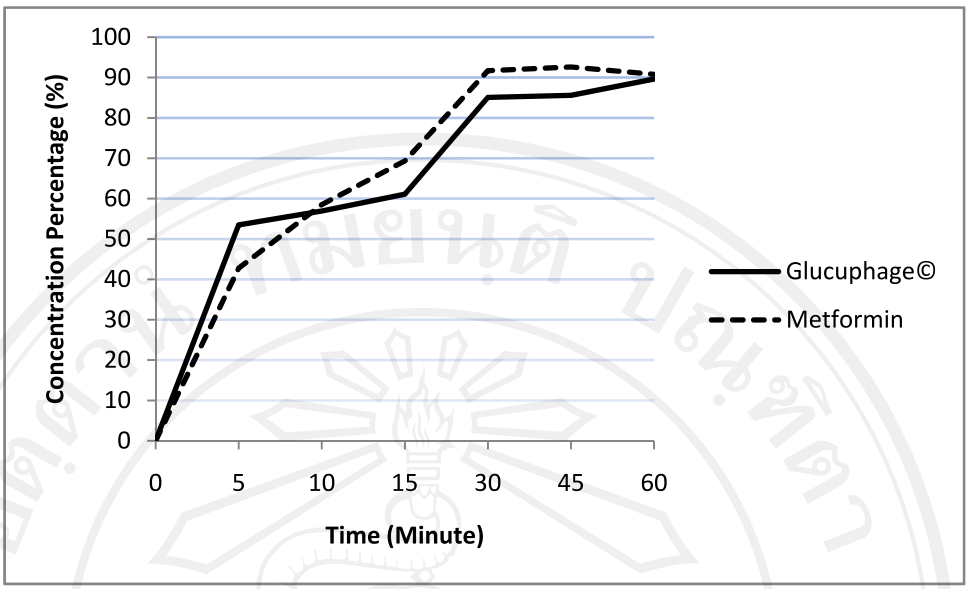

Figure 4.5 The dissolution profile of Glucophage® tablet and metformin hydrochloride tablet

Table 4.5 The comparison of dissolution profile and pharmaceutical equivalence between Glucophage® tablet and metformin hydrochloride tablet

Dissolution profile(%) at time 5/10/15/30/45/60 minute		**Pharmaceutical Equivalence**	
Glucophage®	**Metformin Hydrochloride**		
53.51	42.75	**Difference Factor (F_1)**	**Similarity Factor (F_2)**
56.92	58.53		
61.10	69.37	8.21	59.62
85.06	91.72		
85.59	92.62	**Pass**(< 15)	**Pass**(> 50)
89.63	90.79		

With Metformin hydrochloride production, the F_1 is 8.21, less than 15 and F_2 is 59.62, more than 50, therefore the produced metformin hydrochloride tablet following the OXPIRT is pharmaceutically equivalent to Glucophage® tablet.

4.1.2 Paracetamol tablet production

From preformulation study, information of paracetamol powder (API) and the original tablet of paracetamol (Tylenol®) are obtained. Information of API is given in Table 4.6 and information of Tylenol® is shown in Table 4.7.

Table 4.6 The information of paracetamol powder (API)

Solubility	Flowability	Stability	
		Temperature	Moisture
Sparingly soluble	Poor	Stable	Stable

Table 4.7 The information of Tylenol® tablet (Product)

Information of Tylenol® tablet	Value
Fracture surface	Rough
API weight (mg.)	500
Tablet weight (mg.)	630
Hardness (kg.)	8.3
Disintegration Time (Sec.)	28
Dissolution profile (%) at time 5/10/15/30/45/60 minute	81.31/89.27/94.22/98.76/98.12/101.98

With the information given in Table 4.6 and Table 4.7, OXPIRT found the relevant knowledge. It includes a list of ingredients and their function. They are represented in ontology instance format in Figure 4.6.

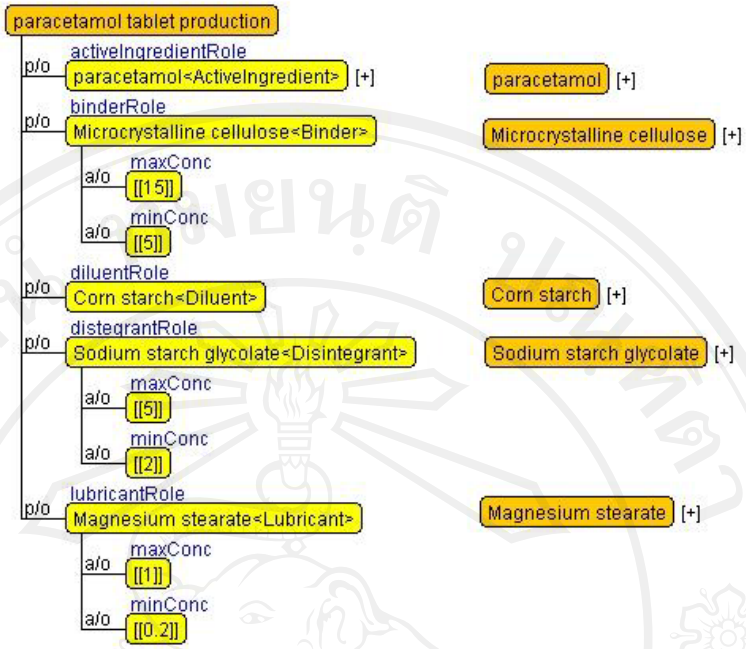

Figure 4.6 The ontology instance of paracetamol tablet production

OXPIRT then applied rules for finding appropriate process. The rule used in this situation is as same as the rule shown in Figure 4.2 because of the same criteria. OXPIRT suggested a wet granulation process for paracetamol tablet production.

After process type was set as wet granulation, OXPIRT inferred a concentration of unknown amount ingredients and later performed a weight calculation based on the assigned concentration and tablet weight. In this case, four ingredients which are microcrystalline cellulose, corn starch, sodium starch glycolate and magnesium stearate were concerned. First, microcrystalline cellulose was involved in the following rule shown in Figure 4.7. With the rule, a concentration of microcrystalline cellulose was inferred to maximum as 15 % and it was computed to weight 94.5 mg.

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>

Figure 4.7 The rule to infer binder concentration for > 5 kg. hardness API

Second, sodium starch glycolate was involved in the following rule shown in Figure 4.8. With the rule, a concentration of sodium starch glycolate was inferred to maximum as 5% and it was computed to weight 31.5 mg.

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 disintegrants at maximum concentration>

Figure 4.8 The rule to infer disintegrant concentration for ≤ 180 seconds disintegration time

Third, magnesium stearate was involved in the following rule shown in Figure 4.9. With the rule, a concentration of magnesium stearate was inferred to maximum as 0.2% and it was computed to weight 0.13 mg.

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>

Figure 4.9 the rule to infer lubricant concentration of sparing soluble, slightly soluble, very slightly soluble and practically insoluble API

Fourth, the diluent amount is computed by the total weight minus the available left space from the already set excipients (i.e., 630 - (500+94.5+31.5+0.13) = 2.7 mg).

Finally, a set of instructions was generated based on rules regarding to the assigned information and previously recommended values. The suggested production for paracetamol is illustrated in Table 4.8.

Table 4.8 The tablet production of paracetamol

	Function	List of excipient	Weight(mg.)
Tablet Formulation	Active ingredient	Paracetamol	500.00
	Binder	Microcrystalline Cellulose	94.50
	Diluent	Corn starch	2.70
	Disintegrant	Sodium starch glycolate	31.50
	Lubricant	Magnesium Stearate	1.30
Manufacturing Instruction	Process type	Wet granulation	
	Instructions	8. Dry mixing metformin hydrochloride, sodium starch glycolate, microcrystalline cellulose, and corn starch. 9. Wet mixing mixture with water until it wet. 10. Communition with sieve no.14 11. Drying 12. Communition with sieve no.18 13. Dry mixing mixture and magnesium stearate 14. Compression	

With formulation and instruction in Table 4.8, the paracetamol tablet is produced. The tablet is then tested for hardness, disintegration time and dissolution profile. Table 4.9 shows the three mentioned test results of the produced tablet.

Table 4.9 The hardness, disintegration time and dissolution profile of Tylenol® and paracetamol tablet

		Tylenol® tablet	Paracetamol Tablet
Hardness (kg.)		8.3	5
Disintegration time (sec.)		28	33
Dissolution Profile (%) At time (minute)	5	81.31	73.01
	10	89.27	82.05
	15	94.22	84.75
	30	98.76	87.25
	45	98.12	91.22
	60	101.98	90.50

Figure 4.10 shows a comparison of dissolution profiles between the paracetamol tablet and the original drug tablet (Tylenol®). Table 4.10 shows a pharmaceutical equivalence result by examining difference factor (F_1) and similarity factor (F_2). With paracetamol production, the F_1 is 9.74, less than 15 and F2 is 53.03, more than 50, therefore the produced paracetamol tablet following the OXPIRT is pharmaceutically equivalent to Tylenol® tablet.

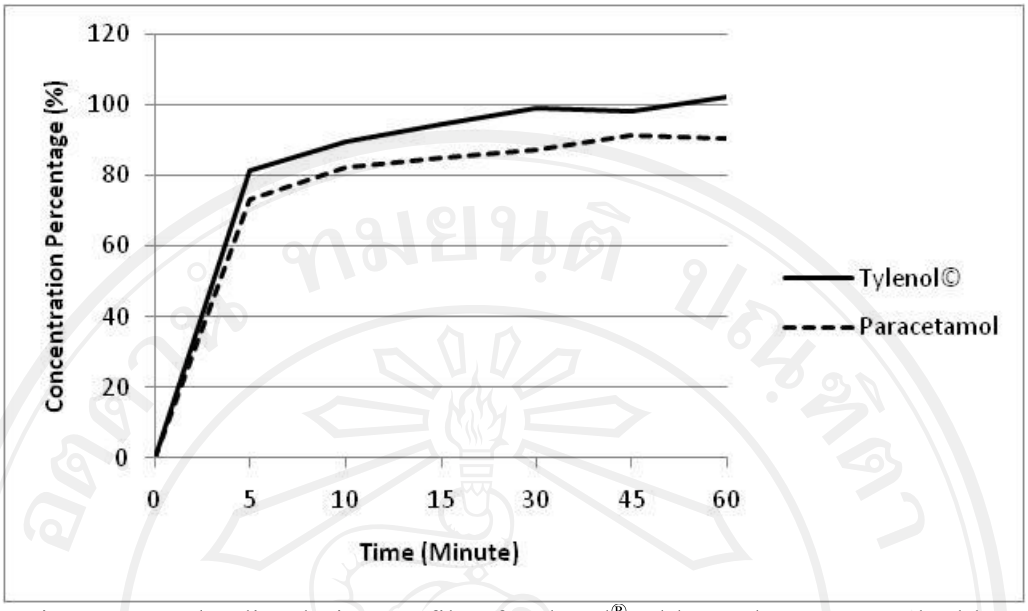

Figure 4.10 The dissolution profile of Tylenol® tablet and paracetamol tablet

Table 4.10 The comparison of dissolution profile and pharmaceutical equivalence between Tylenol® tablet and paracetamol tablet

Dissolution profile(%) at time 5/10/15/30/45/60 minute		**Pharmaceutical Equivalence**	
Tylenol®	**Paracetamol**		
81.31	73.01	**Difference Factor (F_1)**	**Similarity Factor (F_2)**
89.27	82.05		
94.22	84.75	9.74	53.03
98.76	87.25		
98.12	91.22	**Pass**(<15)	**Pass**(> 50)
101.98	90.50		

4.1.3 Hydroxyzine hydrochloride tablet production

From preformulation study, information of hydroxyzine hydrochloride powder (API) and the original tablet of hydroxyzine hydrochloride (Atarax®) are obtained.

Information of API is given in Table 4.11 and information of the original tablet (Atarax®) is shown in Table 4.12.

Table 4.11 The information of hydroxyzine hydrochloride powder (API)

Solubility	Flowability	Stability	
		Temperature	Moisture
Very soluble	Poor	Stable	Stable

Table 4.12 The information of Atarax® tablet (Product)

Information of Atarax® tablet	Value
Fracture surface	Rough
API weight (mg)	10
Tablet weight (mg)	65
Hardness (kg.)	2.3
Disintegration Time (Sec)	180
Dissolution profile(%) at time 5/10/15/30/45/60 minute	25.40/52.75/71.25/96.99/101.66/101.06

With the information given in Table 4.11 and Table 4.12, system searched through the knowledge and returned a list of ingredients and their function represented in ontology instance sketched in Figure 4.11.

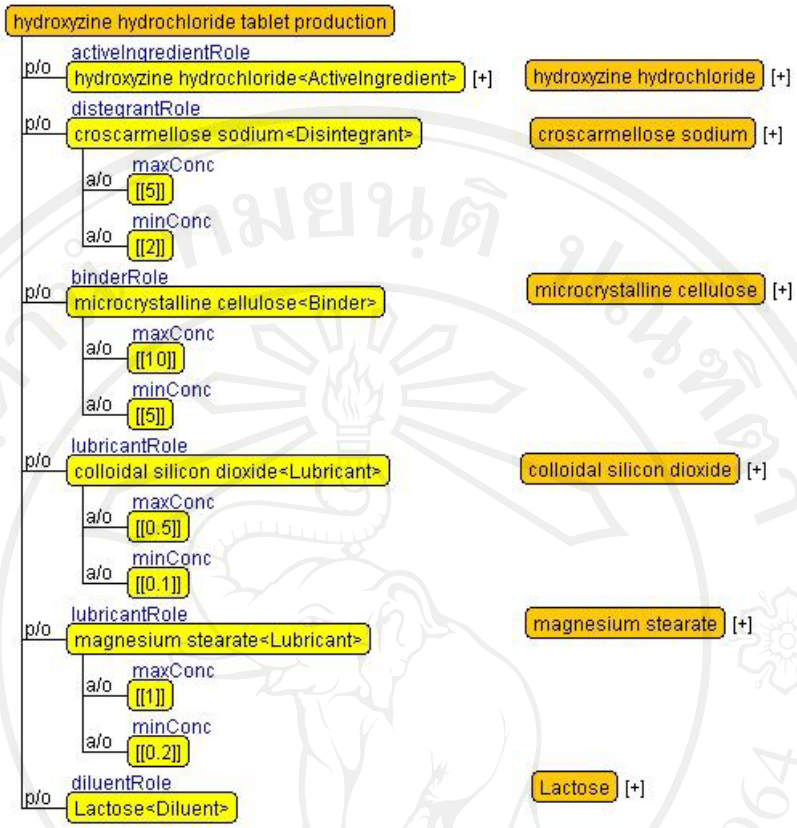

Figure 4.11 The ontology instance of hydroxyzine hydrochloride tablet production

System then applied rules for finding appropriate process. Once again, the same criteria are required; therefore, the rule in Figure 4.2 was applied.

After process type was set as wet granulation, OXPIRT inferred a concentration of excipients and later performed a weight calculation based on the assigned concentration and tablet weight. In this case, five ingredients which are croscarmellose sodium, microcrystalline cellulose, colloidal silicon dioxide, magnesium stearate, and lactose were concerned. First, croscarmellose sodium was involved in the following rule shown in Figure 4.7. With the rule, a concentration of croscarmellose sodium was inferred to maximum as 5 % and it was computed to weight 3.25 mg. Second, microcrystalline cellulose was involved in the following rule

shown in Figure 4.12. With the rule, a concentration of microcrystalline cellulose was inferred to maximum as 10 % and it was computed to weight 6.5 mg.

IF <hardness of the original is between 2.0 and 5.0 kg>
AND <type of binder is hardest>
THEN <set the concentration of binders at medium concentration>

Figure 4.12 The rule to infer binder concentration for hardness between 2-5 kg. product tablet

Third, colloidal silicon dioxide and magnesium stearate were involved in the following rule shown in Figure 4.9. With the rule, a concentration of colloidal silicon dioxide was inferred to minimum as 0.1 % and it was computed to weight 0.07 mg. And a concentration of magnesium stearate was inferred to minimum as 0.2 % and it was computed to weight 0.13 mg.

Fourth, the diluent amount is computed by the total weight minus the available left space from the already set ingredients (i.e., 65-(10+3.25+6.5+0.07+0.13) = 45.05 mg).

Finally, OXPIRT suggested a production for Hydroxyzine hydrochloride as shown in Table 4.13.

Table 4.13 The tablet production of hydroxyzine hydrochloride

	Function	List of excipient	Weight(mg.)
Tablet Formulation	Active ingredient	Hydroxyzine hydrochloride	10.00
	Disintegrant	Croscarmellose sodium	3.25
	Binder	Microcrystalline cellulose	6.50
	Diluent	Lactose	45.05
	Lubricant	Colloidal silicon dioxide	0.07
	Lubricant	Magnesium Stearate	0.13
Manufacturing Instruction	Process type	Wet granulation	
	Instructions	15. Dry mixing hydroxyzine hydrochloride, croscarmellose sodium, microcrystalline cellulose and lactose. 16. Wet mixing mixture with water until it wet. 17. Communition with sieve no.14 18. Drying 19. Communition with sieve no.18 20. Dry mixing mixture, colloidal silicon dioxide and magnesium stearate 21. Compression	

With formulation and instruction in Table 4.13, the hydroxyzine hydrochloride tablet is produced. The tablet is then tested for hardness, disintegration time and dissolution profile. Table 4.14 shows the three mentioned test results of the produced tablet.

Table 4.14 The hardness, disintegration time and dissolution profile of Atarax® tablet and hydroxyzine hydrochloride tablet

		Atarax® tablet	**Hydroxyzine hydrochloride Tablet**
Hardness (kg.)		2.3	2.2
Disintegration time (sec.)		180	200
Dissolution Profile (%) At time (minute)	5	25.40	28.24
	10	52.75	54.71
	15	71.25	81.77
	30	96.99	93.77
	45	101.66	100.65
	60	101.06	103.30

Figure 4.13 shows a comparison of dissolution profiles between the hydroxyzine hydrochloride tablet and the original drug tablet (Atarax®). Table 4.15 shows a pharmaceutical equivalence result by examining difference factor (F_1) and similarity factor (F_2). With hydroxyzine hydrochloride production, the F_1 is 4.79, less than 15 and F_2 is 67.44, more than 50, therefore the produced hydroxyzine hydrochloride tablet following the OXPIRT is pharmaceutically equivalent to Atarax® tablet.

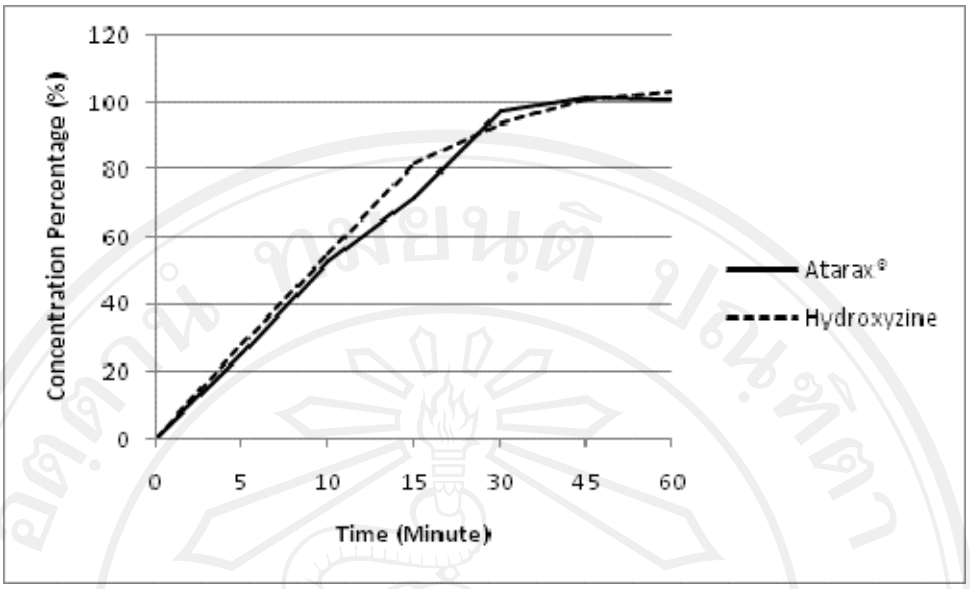

Figure 4.13 The dissolution profile of Atarax® tablet and hydroxyzine hydrochloride tablet

Table 4.15 The Comparison dissolution profile and pharmaceutical equivalence between Atarax® tablet and hydroxyzine hydrochloride tablet

Dissolution profile(%) at time 5/10/15/30/45/60 minute		**Pharmaceutical Equivalence**	
Atarax®	**Hydroxyzine**		
25.40	28.24	**Difference Factor (F_1)**	**Similarity Factor (F_2)**
52.75	54.71		
71.52	81.77	4.79	67.44
96.99	93.77		
101.66	100.65	**Pass** (< 15)	**Pass** (> 50)
101.06	103.3		

4.1.4 Atorvastatin calcium tablet production

From preformulation study, information of atorvastatin calcium powder (API) and the original tablet of atorvastatin calcium (Lipitor®) are obtained. Information of API is given in Table 4.16 and information of the original tablet (Lipitor®) is shown in Table 4.17.

Table 4.16 The information of atorvastatin calcium powder (API)

Solubility	**Flowability**	**Stability**	
		Temperature	**Moisture**
Very slight soluble	Fair	Stable	Stable

Table 4.17 The information of Lipitor® tablet (Product)

Information of Lipitor® tablet	**Value**
Fracture surface	Rough
API weight (mg)	20
Tablet weight (mg)	300
Hardness (kg.)	5.2
Disintegration Time (Sec)	50
Dissolution profile(%) at time 5/10/15/30/45/60 minute	91.08/98.37/101.04/101.07/101.28/101.20

With the information given in Table 4.16 and Table 4.17, system searched through the knowledge and returned a list of ingredients and their function represented in ontology instance sketched in Figure 4.14.

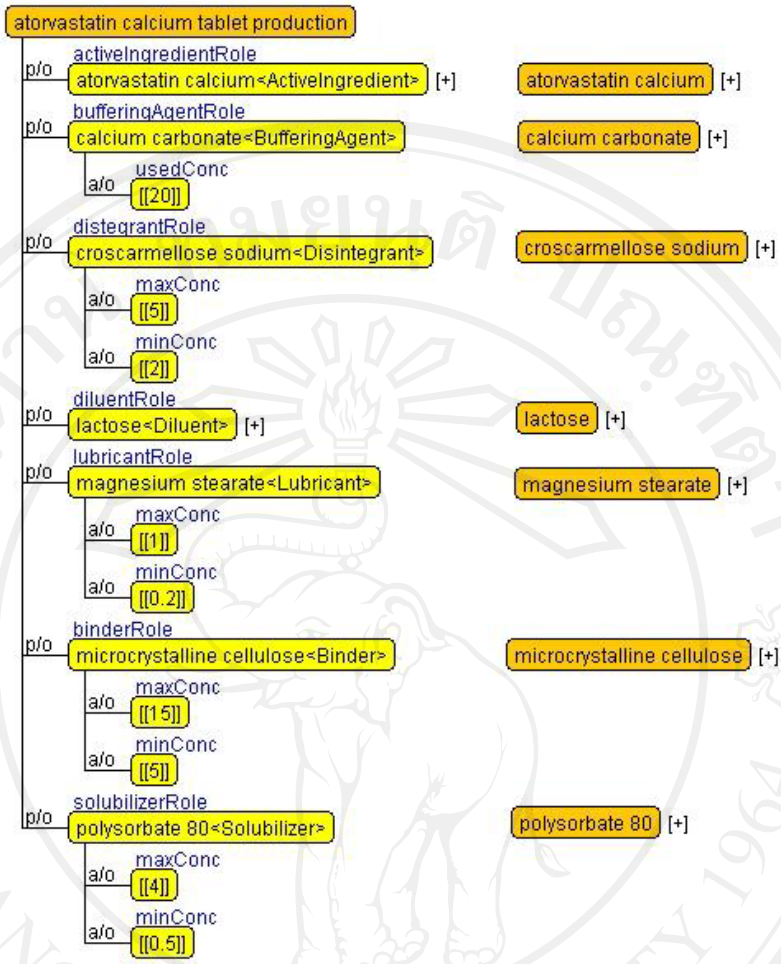

Figure 4.14 The ontology instance of atorvastatin tablet production

System then applied rules for finding appropriate process. The rule used in this situation is shown in Figure 4.15. For literary, since the flowability of API is fair and the compressibility of this API is poor, OXPIRT chose a wet granulation process for this drug production.

IF < API concentration is less than 10%>
THEN < set the process type as Wet granulation >

Figure 4.15 The rule to infer a wet granulation process for >10% concentration API

After process type was set, OXPIRT inferred a concentration of unknown amount ingredients and later performed a weight calculation based on the assigned

concentration and tablet weight. In this case, six ingredients which are calcium carbonate, croscarmellose sodium, lactose, magnesium stearate, microcrystalline cellulose, and Polysorbate 80 were concerned. First, calcium carbonate is set to 20% for buffering agent from literature review. Second, croscarmellose sodium was involved in the following rule shown in Figure 4.8. With the rule, a concentration of croscarmellose sodium was inferred to maximum as 5 % and it was computed to weight 15 mg. Third, microcrystalline cellulose involved in the following rule shown in Figure 4.7. With the rule, a concentration of microcrystalline cellulose was inferred to maximum as 15 % and it was computed to weight 45 mg. Fourth, magnesium stearate involved in the following rule shown in Figure 4.9. With the rule, a concentration of magnesium stearate was inferred to minimum as 0.2 % and it was computed to weight 0.6 mg. Fifth, a concentration of solubilizer tween80 is allocated to maximum following the rule in Figure 4.16. Last, the diluent amount is computed by the total weight minus the available left space from the already set ingredients (i.e., 300 - (20+60+15+45+0.6+12) = 159.4 mg).

IF < solubility of API is sparing soluble, slightly soluble, very slightly soluble, or practically insoluble>
THEN <set the concentration of solubilizer at maximum>

Figure 4.16 the rule to infer solubilizer concentration for sparing soluble, slightly soluble, very slightly soluble, and practically insoluble API

Finally, a set of instructions was generated based on rules shown in Figure 4.17 regarding to the assigned information and previously recommended values. In Table 4.18, all information for production is concluded.

IF <solubilizer exists in formulation >
AND <process type is the wet granulation>
THEN <perform dry-mixing unit operation between API and lubricant>
THEN <perform dry-mixing unit operation between dry-mixed mixture and other excipients>
THEN < perform wet-mixing unit operation of the dry-mixed mixture with water >
THEN < perform drying unit operation>
THEN < perform resizing unit operation with sieve no. 20>
THEN <perform dry-mixing unit operation of resized mixture with lubricants >
THEN <perform compression unit operation to dry-mixed mixture for at least 5 kg or near hardness of the original tablet>

Figure 4.17 The rule to infer instructions of wet granulation process for existing solubilizer in formulation

Table 4.18 The tablet production of 1st atorvastatin calcium

	Function	List of excipient	Weight(mg.)
Tablet Formulation	Active ingredient	Atorvastatin calcium	20.00
	Buffering agent	Calcium carbonate	60.00
	Disintegrant	Croscarmellose sodium	15.00
	Binder	Microcrystalline cellulose	45.00
	Diluent	Lactose	147.40
	Lubricant	Magnesium Stearate	0.6
	Solubilizer	Polysorbate 80	12.00
Manufacturing Instruction	Process type	Wet granulation	
	Instructions	22. Wet mixing atorvastatin calcium and polysorbate 80. 23. Dry mixing mixture with croscarmellose sodium, microcrystalline cellulose, calcium carbonate and lactose. 24. Wet mixing mixture with water until it wet. 25. Communition with sieve no.14 26. Drying 27. Communition with sieve no.18 28. Dry mixing mixture and magnesium stearate 29. Compression	

Figure 4.17 The rule to infer instructions of wet granulation process for existing solubilizer in formulation

Table 4.18, the 1st atorvastatin tablet is produced. The tablet is then tested for hardness, disintegration time and dissolution profile. Table 4.19 shows the three mentioned test results of the produced tablet.

Table 4.19 The hardness, disintegration time and dissolution profile of 1st atorvastatin calcium tablet

		Lipitor® tablet	**1st Atorvastatin calcium Tablet**
Hardness (kg.)		5.2	5.0
Disintegration time (sec.)		50	193
Dissolution Profile (%) At time (minute)	5	91.08	54.05
	10	98.37	61.75
	15	101.40	64.25
	30	101.07	65.22
	45	101.28	65.50
	60	101.20	66.38

Figure 4.18 shows a comparison of dissolution profiles between the 1st atorvastatin tablet and the original drug tablet (Lipitor®). Table 4.20 shows a pharmaceutical equivalence result by examining difference factor (F_1) and similarity factor (F_2). With atorvastatin calcium production, the F_1 is 36.51, more than 15 and F_2 is 23.75, less than 50, therefore the 1st produced atorvastatin calcium tablet following the OXPIRT is not pharmaceutically equivalent to Lipitor® tablet.

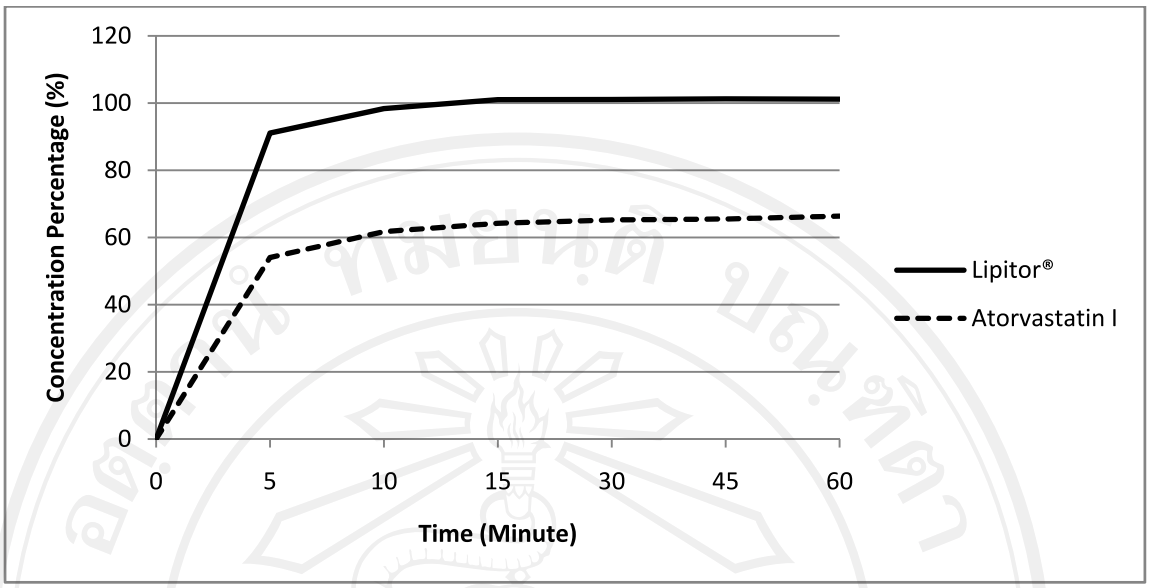

Figure 4.18 The dissolution profile of Lipitor® tablet and the 1st atorvastatin calcium tablet

Table 4.20 The comparison of dissolution profile and pharmaceutical equivalence between Lipitor® tablet and the 1st atorvastatin tablet

Dissolution profile(%) at time 5/10/15/30/45/60 minute		**Pharmaceutical Equivalence**	
Lipitor®	**Atorvastatin**		
91.08	54.05	**Difference Factor (F_1)**	**Similarity Factor(F_2)**
98.37	61.75		
101.04	64.25	36.51	23.75
101.07	65.22		
101.28	65.50	**Not pass** (< 15)	**Not Pass** (>50)
101.20	66.38		

Since neither factors passed the acceptable value, all information with additional hardness, disintegration time and dissolution profile of non-equivalent 1st tablet was resent to OXPIRT again. To improve a dissolution profile, additional rules

in adjustment module were applied accordingly to adapt the previous recommendation. From a flow to improve recommendation result in Section 3.2, the system modified a formulation in two points; not in range dissolution profile and disintegration time.

The system tried to improve dissolution profile which is lower than expected point. From Figure 3.5, the executed path is shown in the left flow in Figure 4.19a. For summary, system sought to add another wetting agent to increase the dissolution profile level. In detail, sodium lauryl sulfate in amount of 3.0 mg. was chosen to add.

For disintegration time problem, the system chose the right flow in Figure 4.19b from entire flow in Figure 3.4 since the conditions are particularly met. It applied a method of increase an amount of another excipient which can be functioned as a disintegrant to improve disintegration time. In depth, the existing binder excipient, microcrystalline cellulose, was scaled up to 75 mg. which is 30 mg. added to function as disintegrant excipient instead.

With both of these methods, 2nd atorvastatin calcium tablet production were returned as shown in Table 4.21

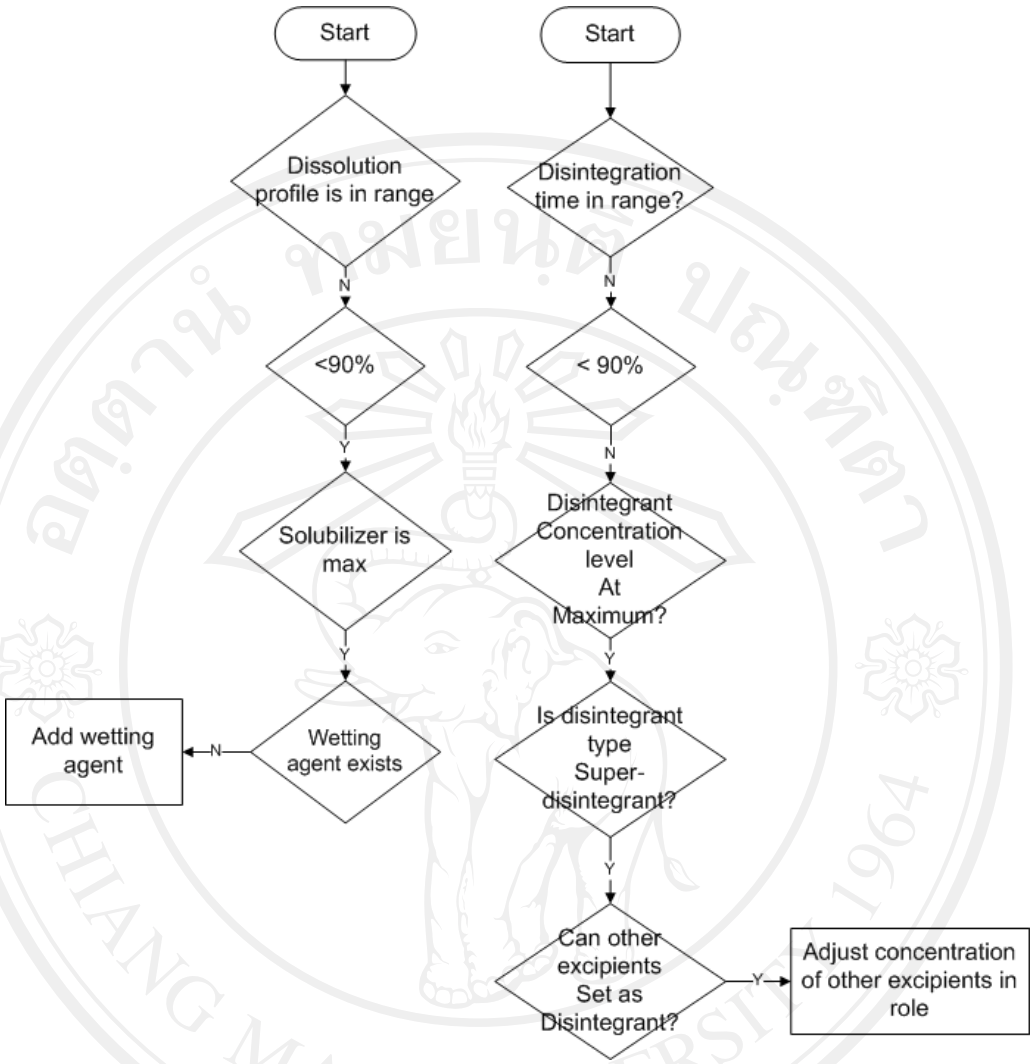

Figure 4.19 The flows of improving an unacceptable result of the 1st atorvastatin tablet

Table 4.21 The 2nd tablet production of atorvastatin calcium

	Function	List of excipient	Weight(mg.)
Tablet Formulation	Active ingredient	Atorvastatin calcium	20.00
	Buffering agent	Calcium carbonate	60.00
	Disintegrant	Croscarmellose sodium	15.00
	Binder	Microcrystalline cellulose	75.00
	Diluent	Lactose	123.40
	Lubricant	Magnesium Stearate	0.60
	Solubilizer	Polysorbate 80	3.00
	Wetting agent	Sodium lauryl sulfate	3.00
Manufacturing Instruction	Process type	Wet granulation	
	Instructions	1. Wet mixing atorvastatin calcium, polysorbate 80 and sodium lauryl sulfate. 2. Dry mixing mixture with croscarmellose sodium, microcrystalline cellulose, calcium carbonate and lactose. 3. Wet mixing mixture 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	

With formulation and instruction in Table 4.21, the 2nd atorvastatin tablet was produced and was resent to test for hardness, disintegration time and dissolution profile again. Table 4.22 shows the three mentioned test results of the produced tablet.

Table 4.22 The hardness, disintegration time and dissolution profile of the 2nd atorvastatin calcium tablet

		Lipitor® tablet	2nd Atorvastatin calcium Tablet
Hardness (kg.)		5.2	5.8
Disintegration time (sec.)		50	59
Dissolution Profile (%) At time (minute)	5	91.08	64.97
	10	98.37	76.48
	15	101.40	77.32
	30	101.07	77.98
	45	101.28	78.12
	60	101.20	78.06

Figure 4.20 shows a comparison of dissolution profiles between the 2nd atorvastatin tablet and the original drug tablet (Lipitor®). Table 4.23 shows a pharmaceutical equivalence result by examining difference factor (F_1) and similarity factor (F_2). With the 2nd atorvastatin calcium production, the F_1 is 23.75, more than 15 and F_2 is 33.05, less than 50, therefore the 2nd produced atorvastatin calcium tablet following the OXPIRT is still not pharmaceutically equivalent to Lipitor® tablet, but the dissolution profile was slightly improved and disintegration time was successfully in acceptable range. The disintegration time of the produced tablet is acceptable when it is in range within 90% to 110% of the disintegration time of the original tablet.

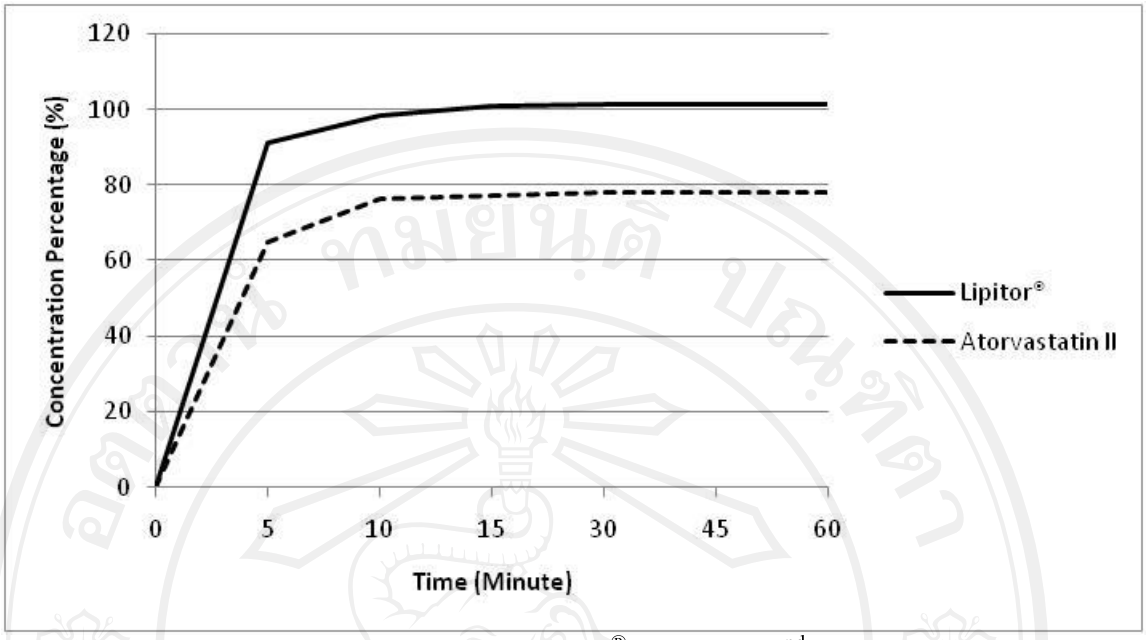

Figure 4.20 The dissolution profile of Lipitor® tablet and 2nd atorvastatin calcium tablet

Table 4.23 The comparison of dissolution profile and pharmaceutical equivalence between Lipitor® tablet and the 2nd atorvastatin tablet

Dissolution profile(%) at time 5/10/15/30/45/60 minute		**Pharmaceutical Equivalence**	
Lipitor®	**Atorvastatin**		
91.08	64.97	Difference Factor (F_1)	Similarity Factor(F_2)
98.37	76.48		
101.04	77.32	23.75	33.05
101.07	77.98		
101.28	78.12	**Not pass**(<15)	**Not Pass** (>50)
101.20	78.06		

Since the dissolution profile was only left to concern, the system tried to improve it by using a decision flow in Figure 3.5 once again. This time, the system applied the adjustment of the wetting agent amount based on conditions following the

path in Figure 4.21. For explanation of X mark in Figure 4.21, the solubilizer was ignored in this alteration because its amount was already modified in the previous recommendation. The system suggested increasing an amount of sodium lauryl sulfate to 6.0 mg. which is raised from previous production by 3.0 mg. in total.

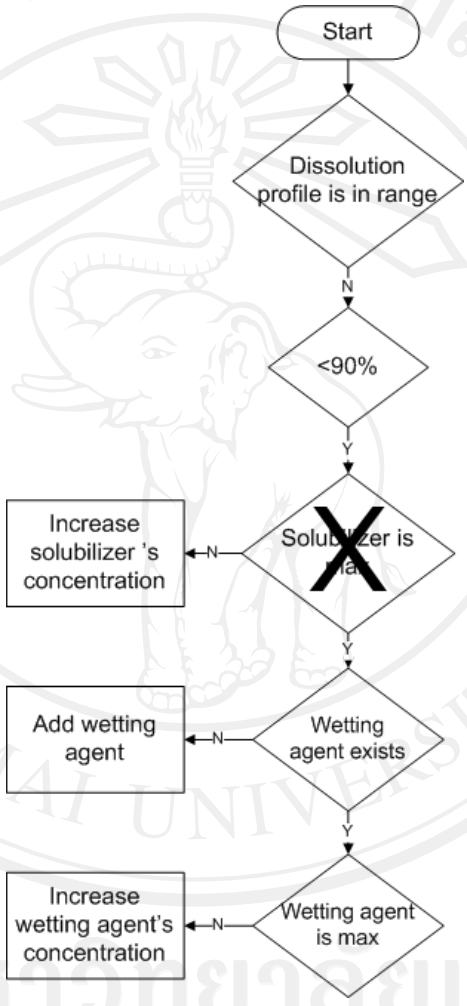

Figure 4.21 The flow of improving an unacceptable result of the 2nd atorvastatin tablet

With the modification of recommendation, a new tablet production of the 3rd atorvastatin calcium is held in Table 4.24.

Table 4.24 The tablet production of the 3rd atorvastatin calcium

	Function	List of excipient	Weight(mg.)
Tablet Formulation	Active ingredient	Atorvastatin calcium	20.00
	Buffering agent	Calcium carbonate	60.00
	Disintegrant	Croscarmellose sodium	15.00
	Binder	Microcrystalline cellulose	75.00
	Diluent	Lactose	117.40
	Lubricant	Magnesium Stearate	0.60
	Solubilizer	Polysorbate 80	3.00
	Wetting agent	Sodium lauryl sulfate	6.00
Manufacturing Instruction	Process type	Wet granulation	
	Instructions	1. Wet mixing atorvastatin calcium, polysorbate 80 and sodium lauryl sulfate. 2. Dry mixing mixture with croscarmellose sodium, microcrystalline cellulose, calcium carbonate and lactose. 3. Wet mixing mixture 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	

With the formulation and instruction in Table 4.24, the 3rd atorvastatin tablet was accordingly produced. All testing processes were committed again and the results are shown in Table 4.25.

Table 4.25 The hardness, disintegration time and dissolution profile of the 3rd atorvastatin calcium tablet

		Lipitor® tablet	3rd Atorvastatin calcium Tablet
Hardness (kg.)		5.2	5.3
Disintegration time (sec.)		50	45
Dissolution Profile (%) At time (minute)	5	91.08	89.91
	10	98.37	100.86
	15	101.40	102.91
	30	101.07	102.86
	45	101.28	103.86
	60	101.20	103.45

Figure 4.22 shows a comparison of dissolution profiles between the 3rd atorvastatin calcium tablet and the original drug tablet (Lipitor®). Table 4.26 shows a pharmaceutical equivalence result by examining difference factor (F_1) and similarity factor (F_2). With the 3rd atorvastatin calcium production, the F_1 is 1.93, less than 15 and F_2 is 84.29, more than 50, therefore the 3rd atorvastatin calcium tablet is finally pharmaceutical equivalent to Lipitor® tablet.

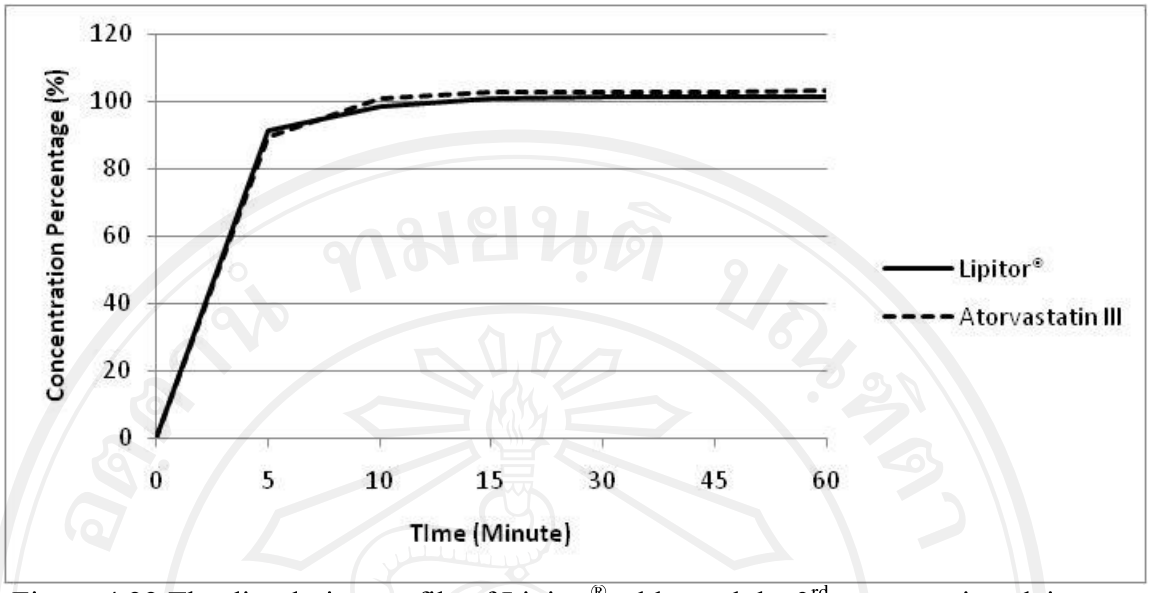

Figure 4.22 The dissolution profile of Lipitor® tablet and the 3rd atorvastatin calcium tablet

Table 4.26 The comparison of dissolution profile and pharmaceutical equivalence between Lipitor® tablet and the 3rd atorvastatin tablet

Dissolution profile(%) at time 5/10/15/30/45/60 minute		**Pharmaceutical Equivalence**	
Lipitor®	**Atorvastatin III**		
91.08	89.81	Difference Factor (F_1)	Similarity Factor (F_2)
98.37	100.86		
101.04	102.91	1.93	84.29
101.07	102.86		
101.28	103.06	**Pass** (<15)	**Pass** (> 50)
101.20	103.45		

4.2 Evaluation result of herbal tablet production from OXPIRT

Two samples of herbal tablet production are selected to evaluate a capability of OXPIRT. In details, a ginger powder and a fa-tha-lai-chon powder are a representative for herbal tablet.

4.2.1 Ginger herbal tablet

Like a generic drug tablet production, it begins with preformulation. The information includes API weight, its flowability and compactability. They are all presented in Table 4.27.

Table 4.27 The information of ginger powder

Herbal weight (mg)	Flowability	Compactability
500	Poor	Poor

With such information from preformulation, OXPIRT decided the process as wet granulation and prompted to add binder, disintegrant and lubricant following the rules in Figure 4.23, Figure 4.24, Figure 4.25 and Figure 4.26 respectively.

IF<flowability of herbal powder is poor, very poor or extremely poor>
AND <compactability of herbal powder is poor or very poor >
THEN< set the process type as Wet granulation >

Figure 4.23 the rule to infer process type for poor flowability and poor compactability herbal powder

IF<flowability of herbal powder is poor>
THEN<set widely used binder type is hard at maximum concentration>

Figure 4.24 The rule to infer binder and its concentration for poor flowability herbal powder

IF<flowability of herbal powder is poor or very poor>
THEN<set widely used disintegrant type is disintegrant at minimum concentration>

Figure 4.25 The rule to infer disintegrant and its concentration for poor flowability herbal powder

IF<for herbal tablet production>
THEN<assign two most selective lubricants and set their concentration at default >

Figure 4.26 The rule to infer lubricants and its concentration for herbal tablet production

For instruction suggestion, the rule is same as the rule mentioned in Figure 4.17. They are all concluded as a recommendation result for ginger herbal tablet production illustrated in Table 4.28.

Table 4.28 The herbal tablet production of ginger powder

	Function	List of excipient	Weight(mg.)
Tablet Formulation	Active ingredient	Ginger powder	500.00
	Binder	Povidone K90	25.00
	Disintegrant	Microcrystalline cellulose	75.00
	Lubricant	Talcum	10
	Lubricant	Magnesium Stearate	5
Manufacturing Instruction	Process type	Wet granulation	
	Instructions	1. Dry mixing ginger powder, povidone K90, and microcrystalline cellulose. 2. Wet mixing mixture with water until it wet. 3. Communition with sieve no.14 4. Drying 5. Communition with sieve no.18 6. Dry mixing mixture, talcum and magnesium stearate 7. Compression	

After producing a tablet based on Table 4.28, it was tested for quality control as given in Table 4.29. The ginger tablet produced following OXPIRT suggestion passes the quality control since all required values are in acceptable range.

Table 4.29 The hardness, disintegration time, weight variation and friability of ginger herbal tablet

Hardness (kg.)	Disintegration Time (sec.)	Weight variation	Friability (%)
3.60	315	1.1635	0.035

4.2.2 Fa-tha-lai-chon herbal tablet

The information of fa-tha-laichon API including weight, flowability and compactability are presented in Table 4.30.

Table 4.30 The information of fa-tha-lai-chon powder

Herbal weight (mg)	Flowability	Compactability
500	Fair	Poor

The process of manufacturing and excipient selection were applied as same as ginger in terms of process, disintegrant and lubricant selection in Figure 4.23, Figure 4.25 and Figure 4.26 respectively, but different rule in Figure 4.27 were exploited for binder type option.

IF<flowability of herbal powder is fair>
THEN< set binder type is soft at maximum concentration >

Figure 4.27 The rule to infer soft type binder and its concentration for fair flowability herbal powder

However, this formulation provided number of excipients in concentration for starch paste is unable to be calculated to weight directly. It depends on volume in wet granulation unit operation which causes lubricants to become undefined amount as

well. Thus, binder and two lubricants in this formulation were stated in concentration instead of weight amount. The generated recommendation is given in Table 4.31.

Table 4.31 The herbal tablet production of fa-tha-lai-chon

	Function	List of excipient	Weight (mg.)	Concentration (%)
Tablet Formulation	Active ingredient	Fa-tha-lai-chon	500.00	
	Binder	Starch paste		10
	Lubricant	Talcum		2
	Lubricant	Magnesium Stearate		1
Manufacturing Instruction	Process type	Wet granulation		
	Instructions	8. Wet mixing fa-tha-lai-chon powder and starch paste until it wet. 9. Communition with sieve no.14 10. Drying 11. Communition with sieve no.18 12. Dry mixing mixture, talcum and magnesium stearate 13. Compression		

After producing a tablet based on Table 4.31, the tablet was tested for quality control as given in. The fa-tha-lai-chon tablet produced following OXPIRT suggestion passes the quality control since all required values are in acceptable range.

Table 4.32 The hardness, disintegration time, weight variation and friability of fa-tha-lai-chon herbal tablet

Hardness (kg.)	Disintegration Time (sec.)	Weight variation	Friability (%)
3.60	213	2.06	0.014

4.3 Discussion

From an evaluation of OXPIRT, it shows promising potential to suggest tablet production. From six samples, five of them were correctly recommended in the first attempt. Another fail sample; however, was later given for the correct formulation and method by the result improvement part. Regarding to the result, it can be claimed that knowledge given in pharmaceutical tablet production ontology (PTPO) and production rule works well with the inference engine.

However, a burden in developing OXPIRT belongs to an expert who fills in information into PTPO and production rule. Though much information is obtained by reviewing the pharmacopoeia and patent, some important information, especially a role of excipient used in tablet formulation, is missed. This information is particularly required in the system. Without it, the system cannot assign an appropriate value for excipients since they can be vary based on the function using in the formulation. For example, micro crystalline cellulose can primarily function as a binder if its concentration is around 5-15%, and it can also act as a disintegrant if its concentration is around 15-40%. Moreover, it can be a diluent either if it is filled lastly to a formulation with any amount. This issue seriously causes very confusing problem to system if the role of excipients in formulation is not specifically provided. Unfortunately, this information can be added by using experience and wise of the expert. Therefore, sooner expired drug patent cannot be suggested by the system since it has never been given in PTPO, or it later requires a burden of expert again to complete such information. Currently, this issue becomes a limitation of the system that can only be applied for already expired drug. To solve such issue in a long term, an automatic role assigner is crucial since role must be assigned alongside the

excipient in formulation and the correctness of role assigning completely reflects the correctness of the recommendation.

In different point of view, role of excipients also lies another issue. From testing, it is obvious that one excipient in formulation has multiple functions within itself. For instance, magnesium stearate is once given into formulation; it contains two different functions as lubricant and anti-adherence in the meantime. Occasionally, some excipients are intentionally chosen for a specific function but its role can be switched to diluent if they are added lastly, e.g., PVP in metformin formulation that is selected for its binder ability but the name for its function is switched to diluent since it fills the rest amount of tablet weight. This is called multi-function circumstance. In actual formulation design, multi-function excipients are often selected since they gives advantage to reduce amount of other chosen excipients or to cut another excipients instead. However, OXPIRT is limited for one role per excipient to prevent confusing in concentration inference. Moreover, the minor function of excipients is not given in PTPO and only major function is particularly focused. It occasionally leads the system to complexity for selecting additional excipient in result improvement module since the relevant information is not provided significantly. Therefore, OXPIRT might try many attempts to randomly select a proper excipient that suits to the wanted function for the appropriate formulation. This issue also reflects a result of herbal tablet production since it is not provided with an original tablet information and list of excipients. Though criteria to select an ingredient function are based on characteristics of API, the excipient selection can be varied due to many available excipients for such function. Occasionally, this issue causes the system to not recommend the best alternative excipient for herbal tablet formulation.

For an overview of PTPO, it and its related production rule were deliberately implemented for tablet production which includes a generic drug tablet and herbal tablet. PTPO was basically designed to serve several information related to tablet dosage form based on ingredient, operation and instruction. To expand the use of this ontology, other dosage forms might be succeeding target. Although it was meant to serve tablet production, a part of ontology that stands for ingredient can directly be applied to other dosage forms, such as capsule and solution, by instantiation the missing ingredients. For other parts, simple expansion of ontology, such as a new unit operation, is required to cover other dosage forms. However, the current production rule using in OXPIRT is the very specific knowledge to tablet production. A new set of production rules must be developed separately for each different dosage form.