## TABLE OF CONTENT


| | Page |
|---|---|
| Acknowledgements | iii |
| English Abstract | iv |
| Thai Abstract | vii |
| List of Tables | xiv |
| List of Figures | xvii |
| CHAPTER 1 INTRODUCTION | 1 |
| 1.1 Statement and significant of the problems | 1 |
| 1.2 Objectives of the study | 3 |
| 1.3 Scope of the study | 4 |
| CHAPTER 2 LITERATURE REVIEW | 5 |
| 2.1 Tablet development and production | 5 |
| 2.1.1 Method of tablet manufacture | 9 |
| 2.1.2 Quality control of tablet | 12 |
| 2.2 A generic drug development | 15 |
| 2.3 Herbal Tablet Production | 18 |
| 2.4 Ontology | 19 |
| 2.4.1 Web Ontology Language | 23 |
| 2.4.2 Hozo Environment | 25 |
| 2.5 Expert System | 28 |
| 2.5.1 Pure production-rule based system | 30 |
| 2.5.2 Rule with knowledge based system | 32 |
| 2.5.2.1 Frame based system | 32 |

**Page**

2.5.2.2 Ontology based system 33

CHAPTER 3 MATERIALS AND METHODS 36

3.1 Development of domain knowledge 36

3.1.1 Design of Ontology 37

3.1.1.1 Class designing 37

3.1.1.2 Relation designing 38

3.1.1.3 Role concept designing 40

3.1.2 Instantiation of Ontology 42

3.2 Development of operation knowledge 43

3.3 OXPIRT system 48

3.3.1 OXPIRT architecture 48

3.3.1.1 Amount adjustment module 50

3.3.1.2 Excipients modification module 50

3.3.1.3 Process generation module 51

3.3.1.4 Pharmaceutical validation module 51

3.3.2 Work Flow of OXPIRT 53

3.3.2.1 Generic drug tablet formulation 54

3.3.2.2 Generic Drug Validation 58

3.3.2.3 Herbal tablet formulation 60

3.4 OXPIRT evaluation method 61

3.4.1 Evaluation of generic drug tablet production 61

3.4.1.1 Materials 62

3.4.1.2 Method for evaluating generic drug tablet production 63

3.4.2 Evaluation of Herbal tablet production 64

**Page**

3.4.2.1 Materials 64

3.4.2.2 Method for evaluating herbal drug tablet production 65

CHAPTER 4 RESULTS AND DISCUSSION 67

4.1 Evaluation result of generic drug tablet production from OXPIRT 67

4.1.1 Metformin hydrochloride tablet production 68

4.1.2 Paracetamol tablet production 73

4.1.3 Hydroxyzine hydrochloride tablet production 78

4.1.4 Atorvastatin calcium tablet production 85

4.2 Evaluation result of herbal tablet production from OXPIRT 100

4.2.1 Ginger herbal tablet 100

4.2.2 Fa-tha-lai-chon herbal tablet 102

4.3 Discussion 104

CHAPTER 5 CONCLUSION 107

REFERENCES 112

APPENDICES 116

APPENDIX A Rules for generating tablet production 117

APPENDIX B Rules for modifying and improving the result 120

CURRICULUM VITAE 121

## LIST OF TABLES


| Table | | Page |
|---|---|---|
| 2.1 | Summary of types and functions of tableting excipients | 7 |
| 2.2 | A comparison of different pharmacopoeial quality control tests | 14 |
| 3.1 | A statistic and a detail of class in PTPO | 42 |
| 3.2 | A set of rules of generating new production of tablet | 44 |
| 3.3 | A set of rules of improving incorrect result | 45 |
| 3.4 | The four testing representatives from two factors | 62 |
| 4.1 | The information of metformin hydrochloride powder (API) | 68 |
| 4.2 | The information of Glucophage® tablet (Product) | 69 |
| 4.3 | The tablet production of metformin hydrochloride | 69 |
| 4.4 | The hardness, disintegration time and dissolution profile of Glucophage® tablet and metformin hydrochloride tablet | 70 |
| 4.5 | The comparison of dissolution profile and pharmaceutical equivalence between Glucophage® tablet and metformin hydrochloride tablet | 72 |
| 4.6 | The information of paracetamol powder (API) | 73 |
| 4.7 | The information of Tylenol® tablet (Product) | 73 |
| 4.8 | The tablet production of paracetamol | 76 |
| 4.9 | The hardness, disintegration time and dissolution profile of Tylenol® and paracetamol tablet | 77 |
| 4.10 | The comparison of dissolution profile and pharmaceutical equivalence between Tylenol® tablet and paracetamol tablet | 78 |
| 4.11 | The information of hydroxyzine hydrochloride powder (API) | 79 |
| 4.12 | The information of Atarax® tablet (Product) | 79 |
| 4.13 | The tablet production of hydroxyzine hydrochloride | 82 |

| Table | | Page |
|---|---|---|
| 4.14 | The hardness, disintegration time and dissolution profile of Atarax® tablet and hydroxyzine hydrochloride tablet | 83 |
| 4.15 | The comparison dissolution profile and pharmaceutical equivalence between Atarax® tablet and hydroxyzine hydrochloride tablet | 84 |
| 4.16 | The information of atorvastatin calcium powder (API) | 85 |
| 4.17 | The information of Lipitor® tablet (Product) | 85 |
| 4.18 | The tablet production of 1st atorvastatin calcium | 88 |
| 4.19 | The hardness, disintegration time and dissolution profile of 1st atorvastatin calcium tablet | 89 |
| 4.20 | The comparison of dissolution profile and pharmaceutical equivalence between Lipitor® tablet and the 1st atorvastatin tablet | 90 |
| 4.21 | The 2nd tablet production of atorvastatin calcium | 93 |
| 4.22 | The hardness, disintegration time and dissolution profile of the 2nd atorvastatin calcium tablet | 94 |
| 4.23 | The comparison of dissolution profile and pharmaceutical equivalence between Lipitor® tablet and the 2nd atorvastatin tablet | 95 |
| 4.24 | The tablet production of the 3rd atorvastatin calcium | 97 |
| 4.25 | The hardness, disintegration time and dissolution profile of the 3rd atorvastatin calcium tablet | 98 |
| 4.26 | The comparison of dissolution profile and pharmaceutical equivalence between Lipitor® tablet and the 3rd atorvastatin tablet | 99 |
| 4.27 | The information of ginger powder | 100 |
| 4.28 | The herbal tablet production of ginger powder | 101 |
| 4.29 | The hardness, disintegration time, weight variation and friability of ginger herbal tablet | 102 |
| 4.30 | The information of fa-tha-lai-chon powder | 102 |

| Table | | Page |
|---|---|---|
| 4.31 | The herbal tablet production of fa-tha-lai-chon | 103 |
| 4.32 | The hardness, disintegration time, weight variation and friability of fa-tha-lai-chon herbal tablet | 103 |

## LIST OF FIGURES


| Figure | | Page |
|---|---|---|
| 2.1 | A flow chart of formulation development process | 8 |
| 2.2 | A wet granulation process | 10 |
| 2.3 | A dry granulation process | 11 |
| 2.4 | A direct compression process | 12 |
| 2.5 | Protocol for reverse engineering | 17 |
| 2.6 | Ontology definition | 20 |
| 2.7 | A Class hierarchy of bicycle concept | 21 |
| 2.8 | Part-whole relations of the bicycle concept | 22 |
| 2.9 | Semantic web's layered architecture | 24 |
| 2.10 | Some part of bicycle ontology in OWL format | 26 |
| 2.11 | A snapshot of the interface of the Hozo ontology editor | 27 |
| 3.1 | An example of a hierarchy | 39 |
| 3.2 | A role concept of disintegrant | 41 |
| 3.3 | An example of a role concept | 41 |
| 3.4 | The instantiation of tablet production | 43 |
| 3.5 | Flowchart of improving disintegration time | 46 |
| 3.6 | Flowchart of improving dissolution profile | 47 |
| 3.7 | A framework of OXPIRT system | 49 |
| 3.8 | A preformulation process by user | 54 |
| 3.9 | A work flow of the system | 55 |
| 3.10 | A user interface for getting the characteristics of original product tablet | 56 |
| 3.11 | An output of tablet production | 57 |

| Figure | | Page |
|---|---|---|
| 3.12 | A user interface for getting testing result of the suggested generic drug tablet | 59 |
| 3.13 | A notification of pharmaceutical equivalence | 59 |
| 4.1 | The ontology instance of metformin hydrochloride tablet | 67 |
| 4.2 | A rule for inference of process type as wet granulation | 68 |
| 4.3 | The rule to infer lubricant concentration of very soluble, freely soluble and soluble API | 70 |
| 4.4 | The rule to infer instructions of wet granulation process for no existing solubilizer in formulation | 71 |
| 4.5 | The dissolution profile of Glucophage® tablet and metformin hydrochloride tablet | 72 |
| 4.6 | The ontology instance of paracetamol tablet production | 74 |
| 4.7 | The rule to infer binder concentration for > 5 kg. hardness API | 75 |
| 4.8 | The rule to infer disintegrant concentration for ≤ 180 seconds disintegration time | 75 |
| 4.9 | The rule to infer lubricant concentration of sparing soluble, slightly soluble, very slightly soluble and practically insoluble API | 75 |
| 4.10 | The dissolution profile of Tylenol® tablet and paracetamol tablet | 78 |
| 4.11 | The ontology instance of hydroxyzine hydrochloride tablet production | 80 |
| 4.12 | The rule to infer binder concentration for hardness between 2-5 kg. product tablet | 81 |
| 4.13 | The dissolution profile of Atarax® tablet and hydroxyzine hydrochloride tablet | 84 |
| 4.14 | The ontology instance of atorvastatin tablet production | 86 |
| 4.15 | The rule to infer a wet granulation process for >10% concentration API | 86 |

| Figure | | Page |
|---|---|---|
| 4.16 | The rule to infer solubilizer concentration for sparing soluble, slightly soluble, very slightly soluble, and practically insoluble API | 87 |
| 4.17 | The rule to infer instructions of wet granulation process for existing solubilizer in formulation | 88 |
| 4.18 | The dissolution profile of Lipitor® tablet and the 1st atorvastatin calcium tablet | 90 |
| 4.19 | The flows of improving an unacceptable result of the 1st atorvastatin tablet | 92 |
| 4.20 | The dissolution profile of Lipitor® tablet and the 2nd atorvastatin calcium tablet | 95 |
| 4.21 | The flow of improving an unacceptable result of the 2nd atorvastatin tablet | 96 |
| 4.22 | The dissolution profile of Lipitor® tablet and the 3rd atorvastatin calcium tablet | 99 |
| 4.23 | The rule to infer process type for poor flowability and poor compactability herbal powder | 100 |
| 4.24 | The rule to infer binder and its concentration for poor flowability herbal powder | 100 |
| 4.25 | The rule to infer disintegrant and its concentration for poor flowability herbal powder | 101 |
| 4.26 | The rule to infer lubricants and its concentration for herbal tablet production | 101 |
| 4.27 | The rule to infer soft type binder and its concentration for fair flowability herbal powder | 102 |