UNIVERSITI PUTRA MALAYSIA

DEVELOPMENT OF HERBAL-BASED ORALLY DISINTEGRATING TABLETS FROM Moringa oleifera Lam. LEAVES

MUHAMMAD AZHAR ALI

FK 2016 148
DEVELOPMENT OF HERBAL-BASED ORALLY DISINTEGRATING TABLETS FROM Moringa oleifera Lam. LEAVES

By

MUHAMMAD AZHAR ALI

Thesis Submitted to the School of Graduate Studies, Universiti Putra Malaysia, in Fulfillment of the Requirements for the Degree of Doctor of Philosophy

December 2016
COPYRIGHT

All material contained within the thesis, including without limitation text, logos, icons, photographs and all other artwork, is copyright material of Universiti Putra Malaysia unless otherwise stated. Use may be made of any material contained within the thesis for non-commercial purposes from the copyright holder. Commercial use of material may only be made with the express, prior, written permission of Universiti Putra Malaysia.

Copyright © Universiti Putra Malaysia
Abstract of thesis presented to the Senate of Universiti Putra Malaysia in fulfillment of the requirement for the Degree of Doctor of Philosophy

DEVELOPMENT OF HERBAL-BASED ORALLY DISINTEGRATING TABLETS FROM Moringa oleifera Lam. LEAVES

By

MUHAMMAD AZHAR ALI

December 2016

Chairman : Associate Professor Yus Aniza Binti Yusof, PhD
Faculty : Engineering

The Moringa oleifera Lam. is a plant from the Moringaceae family. There are about 13 species of the Moringaceae family, of which Moringa oleifera is the species most widely known. It is native to Hamalian regions of Pakistan, India. Moringa. Moringa oleifera leaves are rich in multivitamins, minerals, carbohydrates, anti-oxidants and amino acids, however, extreme bitter taste has caused its low acceptability. The aim of present study was to convert whole Moringa leaves as one of the advanced forms of pharmaceutical dosage such as the orally disintegrating tablet (ODT). In this purpose, Moringa leaves were dried under six different drying conditions as to study the effect of sunlight, drying duration and temperature on vitamins concentration and colour quality. Oven 50 °C drying treatment was found to be optimum in terms of best curve fitting of moisture ratio models, vitamins preservation and colour quality. The dried leaves were ground and the effect of moisture contents, particles shape and size on physical and flow properties of Moringa leaves powder were analysed using Box-Behnken technique. Moringa leaves powder prepared with a hammer mill having 5% moisture contents and 50 μm particles were selected as the optimum on the basis of flowability standards. A correlation (CoI = 0.26CI – 5.47) was established between conventional (Carr Index) and advanced (Cohesion Index) methods for measuring flowability of powders. Banana powder was used as natural superdisintegrant which is one of the main excipient in ODT. The banana powder was prepared using convection oven at 70 °C of 4 mm slice thickness. A comprehensive comparison of prepared banana powder with one of the most commonly used synthetic superdisintegrant, AcDiSol was also done to study its flowability, hardness and disintegration characteristics. Banana powder has superior disintegration properties than AcDiSol but lower in tensile strength. In present formulation, banana
powder acts not only as superdisintegrant but also as flavouring and nutritious agent. The excipients, such as microcrystalline cellulose (MCC), mannitol, aspartame and vanilla were selected as binder, sweeteners and flavouring agents on the basis of their flowability, hardness and taste masking properties. Simplex Lattice Design of Design of Expert® 8.0 software was used to formulate mixtures of Moringa orally disintegrating tablets. Formulation contained Moringa leaves powder (40%), banana powder (10%), MCC (20%), mannitol (20%), aspartame (5%) and vanilla powder (5%) was selected as an optimum on the basis of Food and Drug Administration (FDA) and The International Pharmacopoeia standards for orally disintegrating tablets. The optimum formulation has hardness, disintegration time and friability of 30.15 N, 50 sec and 0.89%, respectively. The dissolution of formulated tablets was tested in distilled water and simulated saliva using dissolution models to study the dissolution behaviour of tablets when mixed with water and swallowed in the mouth. Korsmeyer-Peppas model described best the dissolution behaviour of Moringa Orally Disintegrating Tablet (MODT). The Korsmeyer $n$ value of optimum MOST was 1.128 in distill water which shows rapid disintegration of formulated tablets. The optimum MODT was found not very stable as it gained 5%-6% weight and hardness was also reduced 85%-100% at 75% relative humidity levels. The acute and sub-acute toxicity of optimum formulation were tested on rabbits and found absolutely safe as no damage were observed in liver and kidney cells of rabbits treated with the highest dosage rate of 250 mg/kg body weight. The total theoretical cost including raw materials and processing of optimum MODT was USD 0.023 which is the lowest for any multivitamins available in the Malaysian market. Five tablets per day of MODT have a moderate amount of minerals, amino acids and can fulfill 100% Recommended Dietary Allowance (RDA) of vitamin A (0.6 mg/day) for adolescence.

The present research work provides a fundamental understanding of tableting characteristics of any herb and medicinal plant leaves powder in their pure form. It is the first report herbal based orally disintegrating tablet of any herbal and leaves powder of medicinal plant in combination with fruit powder.
Abstrak tesis yang dikemukakan kepada Senat Universiti Putra Malaysia sebagai memenuhi keperluan untuk Ijazah Doktor Falsafah

PEMBANGUNAN HERBA-BASED SECARA LISAN BERPECAH BELAH TABLET DARI Moringa oleifera Lam. DAUN

Oleh

MUHAMMAD AZHAR ALI

Disember 2016

Pengerusi : Profesor Madya Yus Aniza Binti Yusof, PhD
Fakulti : Kejuruteraan

Moringa oleifera Lam. adalah tumbuhan yang berasal daripada keluarga Moringaceae. Terdapat kira-kira 13 spesies keluarga Moringaceae, di mana Moringa oleifera adalah spesies yang paling terkenal. Ia berasal dari kawasan Hamalian daripada Pakistan, India. Daun Moringa oleifera kaya dengan multivitamin, mineral, karbohidrat, anti-oksida dan asid amino, bagaimanapun, rasa pahitnya yang melampau telah menyebabkan ia mendapat penerimaan yang rendah. Tujuan kajian ini adalah untuk menukar keseluruhan daun Moringa sebagai salah satu bentuk dos farmaseutikal yang maju seperti pil perpecahan unggul (ODT). Dalam kajian ini, daun Moringa telah dikeringkan menggunakan enam jenis pengeringan yang berbeza bagi mengkaji kesan cahaya matahari, tempoh pengeringan dan suhu terhadap kepekatan vitamin dan kualiti warna. Rawatan pengeringan ketuhar pada 50 °C didapati optimum dari segi model lengkung sesuai terbaik nisbah kelembapan, vitamin pemeliharaan dan kualiti warna. Daun-daun kering tersebut dikisar dan kepelbagaian kelembapan, saiz dan bentuk zarah pada sifat-sifat fizikal dan aliran serbuk daun Moringa dianalisis dengan menggunakan teknik Box Behnken. Serbuk daun Moringa yang disediakan menggunakan tukul kilang yang mempunyai 5% kelembapan dan 50 mikron zarah telah dipilih sebagai nilai optimum berdasarkan piawaian kebolehaliran. Korelasi (Col = 0.26CI - 5.47) telah dibina antara kaedah konvensional (Indeks Carr) dan maju (Indeks perpaduan) untuk mengira kebolehaliran serbuk. Serbuk pisang telah digunakan sebagai bahan perpecahan unggul semula jadi yang merupakan salah satu daripada ekspi penama utama di ODT. Serbuk pisang telah disediakan dengan menggunakan ketuhar perolakan pada suhu 70 °C dan ketebalan keping 4 mm. Perbandingan menyeluruh serbuk pisang dengan salah satu daripada perpecahan unggul sintetik yang paling biasa
digunakan, AcDiSol juga telah dilakukan untuk mengkaji ciri-ciri kebolehaliran, kekerasan dan perpecahan. Serbuk pisang mempunyai ciri-ciri pecahan unggul daripada AcDiSol tetapi lebih rendah dalam kekuatan tegangan. Dalam penggubalan formulasi ini, serbuk pisang bukan sahaja bertindak sebagai perpecahan unggul tetapi juga sebagai perasa dan ejen berkhasiat. Eksipien, seperti microcrystalline cellulose (MCC), mannitol, aspartame dan vanila telah dipilih sebagai pengikat, pemanis dan ejen perasa atas dasar kebolehaliran mereka, kekerasan dan sifat rasa pelekat. Simplex kekisi Reka bentuk perisian Expert® 8.0 telah digunakan untuk merumuskan campuran pil Moringa mudah larut. Formula yang terkandung pada serbuk daun Moringa (40%), serbuk pisang (10%), MCC (20%), mannitol (20%), aspartame (5%) dan serbuk vanila (5%) telah dipilih sebagai optimum atas dasar Pentadbiran makanan dan Dadah (FDA) dan piawaian Antarabangsa farmakope untuk pil perpecahan unggul. Penggubalan optimum mempunyai kekerasan, masa kehancuran dan kerapuhan masing-masing pada 30.15 N, 50 saat dan 0.89%. Pembubaran pil formulasi telah diuji di dalam air suling dan simulasi air liur menggunakan model pembubaran untuk mengkaji tingkah laku pembubaran pil apabila dicampur dengan air dan ditelan dalam mulut. Model Korsmeyer-Peppas menggambarkan tingkah laku terbaik bagi pembubaran pil perpecahan unggul Moringa (MODT). Nilai Korsmyer-Peppas \( n \) bagi optimum MODT adalah 1.128 dalam air suling yang menunjukkan perpecahan pesat pil formulasi. Optimum MODT optimum didapati tidak berapa stabil kerana pertambahan berat sebanyak 5%-6% dan kekerasan juga berkurang daripada 85% -100% kepada 75% tahap kelembapan relatif. Ketoksikan akut dan sub-akut penggubalan optimum telah diuji pada arnab dan mendapati ia benar-benar tidak ada kerosakan diperhatikan dalam sel-sel hati dan buah pinggang arnab yang dirawat dengan pada kadar dos berat badan tertinggi 250 mg/kg. Jumlah kos teori termasuk bahan-bahan mentah dan pemprosesan optimum MODT adalah USD 0.023 dan ia adalah yang paling rendah bagi mana-mana multivitamin yang terdapat di pasaran Malaysia. Lima biji pil MODT sehari mempunyai jumlah mineral dan asid amino yang sederhana dan dapat memenuhi 100% Recommended Dietary Allowance (RDA) vitamin A (0.6 mg/hari) bagi remaja.

Kerja-kerja penyelidikan semasa ini memberikan asas kefahaman mengenai ciri-ciri sebarang pil herba dan serbuk daun tumbuhan ubatan dalam bentuk tulen. Ia adalah pil perpecahan unggul berasaskan herba yang pertama daripada serbuk herba dan daun tumbuhan ubatan dengan kombinasi serbuk buah-buahan.
ACKNOWLEDGEMENTS

Allah Almighty is always beneficent and affectionate to mankind, that’s why according to his words every piece of work is rewarded according to the devotion and dedication incorporated in it. Like every humble particle of his kingdom, I am also thankful to Allah Almighty for his blessings, the Lord who bestowed me with the potential and fondness to complete this research. No doubt, this kindness is infinite. I present my humblest and wet eyed thanks from the core of my heart to the Holy Prophet Muhammad (Sallallahu alaihi wa-alaihi wasallam), the greatest man who ever walked on the earth, a permanent source of inspiration and guidance for the mankind.

I wish to record my sincerest appreciations to my supervisor Dr. Yus Aniza Yusof, Associate Professor, Department of Process and Food Engineering, Universiti Putra Malaysia, for her advice, supervision, criticism and encouragement throughout the course of my studies. I feel much honor to complete my research work under her enthusiastic guidance and sympathetic attitude, inexhaustible inspiration and enlightened supervision. She opened new doors for me in the field of Food Engineering. I am thankful to my supervisor for her encouragement to me without her help it was difficult for me.

I also express deep my gratitude to Ir. Dr. Chin Nyuk Ling, Associate Professor, Department of Process and Food Engineering, Universiti Putra Malaysia, for her constructive criticism, valuable suggestions and encouragements to improve this manuscript. I am also thankful to Dr. Mohammad Noordin Ibrahim, Associate Professor, Department of Process and Food Engineering, Universiti Putra Malaysia, for his valuable comments and guidance.

I owe a lot to my family members especially my Father, Muhammad Ali, (1st Class Boiler Engineer and Mechanical Engineer) and my wife Dr. Sadaf Muneer (MBBS) for their prayers, support and best wishes. It is not fair if I do not remember my Mother Amna Ali, who had always been encouraging me.

Muhammad Azhar Ali
I certify that a Thesis Examination Committee has met on 16 December 2016 to conduct the final examination of Muhammad Azhar Ali on his thesis entitled "Development of Herbal-Based Orally Disintegrating Tablets from Moringa oleifera Lam. Leaves" in accordance with the Universities and University Colleges Act 1971 and the Constitution of the Universiti Putra Malaysia [P.U.(A) 106] 15 March 1998. The Committee recommends that the student be awarded the Doctor of Philosophy.

Members of the Thesis Examination Committee were as follows:

Mohd Shamsul bin Anuar, PhD
Senior Lecturer
Faculty of Engineering
Universiti Putra Malaysia
(Chairman)

Rosnah binti Shamsudin, PhD
Associate Professor
Faculty of Engineering
Universiti Putra Malaysia
(Internal Examiner)

Rosnita binti A.Talib, PhD
Associate Professor
Faculty of Engineering
Universiti Putra Malaysia
(Internal Examiner)

Wanderley Pereira Oliveira, PhD
Professor
University of Sao Paulo
Brazil
(External Examiner)

NOR AINI AB. SHUKOR, PhD
Professor and Deputy Dean
School of Graduate Studies
Universiti Putra Malaysia

Date: 26 January 2017
This thesis was submitted to the Senate of the Universiti Putra Malaysia and has been accepted as fulfillment of the requirement for the degree of Doctor of Philosophy. The members of the Supervisory Committee were as follows:

**Yus Aniza Binti Yusof, PhD**  
Associate Professor  
Faculty of Engineering  
Universiti Putra Malaysia  
(Chairman)

**Chin Nyuk Ling, PhD**  
Professor  
Faculty of Engineering  
Universiti Putra Malaysia  
(Chairman)

**Mohd. Noordin Ibrahim, PhD**  
Associate Professor  
Faculty of Engineering  
Universiti Putra Malaysia  
(Chairman)

---

**ROBIAH BINTI YUNUS, PhD**  
Professor and Dean  
School of Graduate Studies  
Universiti Putra Malaysia

Date:
Declaration by graduate student

I hereby confirm that:
• this thesis is my original work;
• quotations, illustrations and citations have been duly referenced;
• this thesis has not been submitted previously or concurrently for any other degree at any institutions;
• intellectual property from the thesis and copyright of thesis are fully-owned by Universiti Putra Malaysia, as according to the Universiti Putra Malaysia (Research) Rules 2012;
• written permission must be obtained from supervisor and the office of Deputy Vice-Chancellor (Research and innovation) before thesis is published (in the form of written, printed or in electronic form) including books, journals, modules, proceedings, popular writings, seminar papers, manuscripts, posters, reports, lecture notes, learning modules or any other materials as stated in the Universiti Putra Malaysia (Research) Rules 2012;
• there is no plagiarism or data falsification/fabrication in the thesis, and scholarly integrity is upheld as according to the Universiti Putra Malaysia (Graduate Studies) Rules 2003 (Revision 2012-2013) and the Universiti Putra Malaysia (Research) Rules 2012. The thesis has undergone plagiarism detection software

Signature: ______________________________    Date: __________________

Name and Matric No.: Muhammad Azhar Ali / GS39817
Declaration by Members of Supervisory Committee

This is to confirm that:

- the research conducted and the writing of this thesis was under our supervision;
- supervision responsibilities as stated in the Universiti Putra Malaysia (Graduate Studies) Rules 2003 (Revision 2012-2013) were adhered to.

Signature: 
Name of Chairman of Supervisory Committee: Associate Professor Dr. Yus Aniza Binti Yusof

Signature: 
Name of Member of Supervisory Committee: Professor Dr. Chin Nyuk Ling

Signature: 
Name of Member of Supervisory Committee: Associate Professor Dr. Mohd. Noordin Ibrahim
# TABLE OF CONTENTS

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABSTRACT</td>
<td>i</td>
</tr>
<tr>
<td>ABSTRAK</td>
<td>iii</td>
</tr>
<tr>
<td>ACKNOWLEDGEMENTS</td>
<td>v</td>
</tr>
<tr>
<td>APPROVAL</td>
<td>vi</td>
</tr>
<tr>
<td>DECLARATION</td>
<td>viii</td>
</tr>
<tr>
<td>LIST OF TABLES</td>
<td>xv</td>
</tr>
<tr>
<td>LIST OF FIGURES</td>
<td>xviii</td>
</tr>
<tr>
<td>LIST OF APPENDICES</td>
<td>xxiii</td>
</tr>
<tr>
<td>LIST OF ABBREVIATIONS</td>
<td>xxv</td>
</tr>
</tbody>
</table>

## CHAPTER

### 1 INTRODUCTION

1.1 *Moringa Oleifera* Tree  
1.1.1 Nutritional Facts of Moringa Leaves  
1.2 Processing of Leaves  
1.2.1 Drying of Leaves  
1.2.2 Powder Formation  
1.2.3 Tablet Formulation and Evaluation  
1.3 Problem Statement and Objectives  
1.4 Scope of Study  
1.5 Research Hypothesis  
1.6 Outline of Thesis

### 2 REVIEW OF LITERATURE

2.1 Introduction  
2.2 Nutritional Facts of Moringa Leaves  
2.3 *Moringa Oleifera* Leaves Products  
2.4 Importance of Vitamins  
2.5 Drying Technologies  
2.5.1 Overall Drying Process  
2.5.2 Factors Affecting on Agricultural Product During Drying  
2.5.3 Drying Kinetics and Thin Layer Drying Models  
2.6 Effects of Drying on Food Quality  
2.7 Physical and Flow Properties of Powder  
2.7.1 Particle Size and Shape  
2.7.2 Carr Index (CI) and Hausner Ratio (HR)  
2.8 Powder Compression Modelling  
2.9 Orally Disintegrating Tablets (ODTs)  
2.9.1 Challenges and Limitations of ODTs


2.9.2 Mechanism of ODTs
2.9.3 Manufacturing Methods

2.10 Excipients used in Formulation of ODTs
2.10.1 Effects of Diluents and Binders
2.10.2 Effects of Disintegrating Agents
2.10.3 Superdisintegrating Agents
2.10.4 Flavours and Sweeteners

2.11 In vitro Evaluation of ODTs
2.11.1 Weight Variation
2.11.2 Hardness, Tensile strength and Friability
2.11.3 Wetting Time
2.11.4 Disintegration Time

2.12 Dissolution Studies
2.12.1 Paddle Type Dissolution Apparatus
2.12.2 Release Kinetics

2.13 Toxicological Studies
2.14 Stability Studies

3 DRYING OF MORINGA LEAVES AND BANANA FRUIT
3.1 Introduction
3.2 Materials
3.3 Drying of Moringa Leaves
3.3.1 Conventional Drying
3.3.2 Oven Drying
3.3.3 Freeze Drying
3.4 Empirical Modelling
3.5 Drying of Banana Slices
3.5.1 Grinding of Banana Slices
3.5.2 Freeze Drying
3.6 Colour Analysis of Moringa Leaves and Banana Slices
3.7 Statistical Analysis
3.8 Vitamins Analysis of Moringa Leaves and Banana Slices
3.8.1 Vitamin A (β-carotene)
3.8.2 B-Complex Vitamins (B1, B2, B3 and B6)
3.8.2.1 Chromatographic Condition
3.8.3 Vitamin C (Ascorbic acid)
3.8.4 Vitamin E (α-Tocopherol)
3.9 Results and Discussion
3.9.1 Drying Behaviour of Moringa Leaves
3.9.2 Thin Layer Drying Modelling
3.9.3 Colour Analysis of Moringa Leaves
3.9.4 Effect of Drying Treatments on Vitamins Concentration of Moringa Leaves
3.9.5 Drying Behaviour of Banana Slices  
3.9.6 Colour Analysis of Banana Slices  
3.9.7 Effect of Drying Treatments on Vitamins Concentration of Banana Slices  

3.10 Summary  

4 PHYSICAL, FLOW AND COMPACTION CHARACTERISTICS OF POWDERS  
4.1 Introduction  
4.2 Materials  
4.3 Physical Properties of Powders  
4.3.1 Bulk Density  
4.3.2 Tapped Density  
4.3.3 Particle Shape  
4.3.4 Sieving of Powder  
4.3.5 Size Determination of Particles  
4.4 Flowability of Powders  
4.4.1 Cohesion Test  
4.4.2 Caking Test  
4.4.3 Powder Flow Speed Dependency (PFSD) Test  
4.4.4 Data Analysis  
4.5 Compressibility of Powders  
4.5.1 Tensile Strength  
4.6 Mathematical Modelling of Powders  
4.6.1 Kawakita and Lüdde Model  
4.6.2 Heckel Model  
4.6.3 Adams Mckeown Model  
4.6.4 Panelli-Filho Model  
4.7 Selection Criteria of Excipients  
4.8 Results and Discussion  
4.8.1 Effect of Grinding on Flowability of MLP  
4.8.1.1 Cohesion Test Analysis  
4.8.1.2 Caking Test Analysis  
4.8.1.3 PFSD Test Analysis  
4.8.2 Physical and Flow Properties of Excipients  
4.8.3 Compression Analysis of Excipients used in MODTs  
4.8.3.1 Kawakita and Lüdde Model  
4.8.3.2 Heckel Model  
4.8.3.3 Adams and Mckeown Model  
4.8.3.4 Panelli-Filho Model  
4.8.4 Tensile Strength of Excipients  
4.9 Summary  

xii
5 FORMULATION AND EVALUATION OF MORINGA ORALLY DISINTEGRATING TABLETS

5.1 Introduction 104

5.2 Materials 104

5.2.1 *Moringa Oleifera* Leaves Powder 104

5.2.2 Superdisintegrants 105

5.2.3 Diluent or Binder 105

5.2.4 Sweeteners 105

5.2.5 Flavouring Agent 106

5.2.6 Simulated Saliva Chemicals 107

5.3 Formulation of Moringa Orally Disintegrating Tablets (MODTs) 107

5.4 Pre-compaction Analysis 107

5.5 Formation of MODTs 108

5.6 Evaluation of MODTs 108

5.6.1 Thickness and Weight Variation 110

5.6.2 Friability 110

5.6.3 Hardness and Tensile Strength 110

5.6.4 Wetting Time 110

5.6.5 *In vitro* Disintegration Time 111

5.6.6 Dissolution Studies 112

5.6.6.1 Dissolution in Distilled Water 113

5.6.6.2 Dissolution in Simulated Saliva 113

5.7 Mathematical Modelling 113

5.7.1 Zero Order Kinetics 114

5.7.2 First Order Kinetics 114

5.7.3 Higuchi Model 114

5.7.4 Hixson-Crowell Model 115

5.7.5 Korsmeyer-Peppas Model 115

5.7.6 Similarity Factor ($f_2$) 116

5.8 Results and Discussion 116

5.8.1 Pre-compaction Analysis of MODT Mixtures 116

5.8.2 Effect of Excipients on Physical and Flow Properties of MODT Mixtures 118

5.8.3 Compression Analysis of Mixtures 121

5.8.4 Evaluation of MODTs 126

5.8.4.1 Weight Variation 126

5.8.4.2 Thickness Variation 126

5.8.4.3 Hardness of Formulated MODTs 127

5.8.4.4 Tensile Strength 131

5.8.4.5 Friability 132

5.8.4.6 Disintegration Time 136

5.8.4.7 Wetting Time 137

5.8.5 Dissolution Studies of MODTs 139
5.8.6 Dissolution Modelling
5.8.6.1 Model Dependent Method
5.8.6.2 Model-independent Method (Similarity and Difference Factor)

5.9 Summary

6 STABILITY, FEASIBILITY AND TOXICOLOGY STUDIES OF OPTIMUM TABLET
6.1 Introduction
6.2 Materials
6.3 Sensory Evaluation of Optimum MODT
6.4 Toxicological Studies
   6.4.1 Histopathological Procedure
      6.4.1.1 Fixation
      6.4.1.2 Dehydration
      6.4.1.3 Sectioning
      6.4.1.4 Staining
      6.4.1.5 Microscopic Examination
6.5 Accelerated Stability Study
   6.5.1 Acceptance Criteria
   6.5.2 Stability Testing
6.6 Results and Discussion
   6.6.1 Sensory Evaluation of Optimum MODT
   6.6.2 Economic Analysis
   6.6.3 Toxicological Studies
      6.6.3.1 Toxicity of Optimum MODT
   6.6.4 Stability Study of Optimum MODT
6.7 Summary

7 CONCLUSIONS AND RECOMMENDATIONS FOR FUTURE WORK
7.1 Conclusions
7.2 Recommendations for Future Research

REFERENCES
APPENDICES
BIODATA OF STUDENT
LIST OF PUBLICATIONS
# LIST OF TABLES

<table>
<thead>
<tr>
<th>Table</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.1</td>
<td>Nutrients range of Moringa leaves reported in different studies.</td>
</tr>
<tr>
<td>2.1</td>
<td>Recommended Dietary Allowance (RDA) of vitamins for the adolescence (FAO, 2001; USDA, 2014).</td>
</tr>
<tr>
<td>2.2</td>
<td>Empirical thin layer moisture ratio models.</td>
</tr>
<tr>
<td>2.3</td>
<td>Excipients used in the formulation of orally disintegrating tablets.</td>
</tr>
<tr>
<td>2.4</td>
<td>Evaluation of different orally disintegrating tablets prepared by direct compression method.</td>
</tr>
<tr>
<td>3.1</td>
<td>Empirical models used for analysing the drying data of Moringa leaves.</td>
</tr>
<tr>
<td>3.2</td>
<td>Statistical analysis of thin layer drying models for Moringa leaves with respect to drying treatments.</td>
</tr>
<tr>
<td>3.3</td>
<td>Vitamins concentration (mg/100g) of Moringa leaves with respect to drying treatments.</td>
</tr>
<tr>
<td>3.4</td>
<td>Vitamins concentration of fresh and dried banana slice.</td>
</tr>
<tr>
<td>4.1</td>
<td>Flowability ranges of Carr Index and Hausner Ratio (Carr, 1965; Hausner, 1967).</td>
</tr>
<tr>
<td>4.2</td>
<td>Powder flowability categorization limits based on cohesion index (PFA, 2015).</td>
</tr>
<tr>
<td>4.3</td>
<td>ANOVA for effect of moisture, particles shape and size on the flowability of MLP.</td>
</tr>
<tr>
<td>4.4</td>
<td>Equations generated by Design of Expert software against CI, Col and MCS of MLP.</td>
</tr>
<tr>
<td>4.5</td>
<td>Physical properties of excipients used in the formulation of MODTIs.</td>
</tr>
</tbody>
</table>
4.6 Flow properties of excipients used in the formulation of MODTs.

4.7 Constants of compression models.

5.1 Minimum and maximum levels of design constraints.

5.2 Formulations of MODTs generated by Design of Expert® 8.0 software.

5.3 ANOVA for Carr Index (CI) and Cohesion Index (CoI) of MODT mixtures.

5.4 Equations for Carr Index (CI) and Cohesion Index (CoI) of MODT mixtures.

5.5 Compression model constant of formulated (F1-F10) mixtures of MODT with banana powder as superdisintegrant.

5.6 Post compression evaluation data of MODTs (banana) at 20 kN.

5.7 Post compression evaluation data of MODTs (AcDiSol) at 20 kN.

5.8 ANOVA for MODTs evaluation parameters with banana powder as natural superdisintegrant.

5.9 Equations for MODTs evaluation parameters with banana powder as natural superdisintegrant.

5.10 ANOVA for MODTs evaluation parameters with AcDiSol as synthetic superdisintegrant.

5.11 Equations for MODTs evaluation parameters with AcDiSol as synthetic superdisintegrant.

6.1 Hedonic scale for sensory evaluation of MODT.

6.2a Ascending grades of alcohol.

6.2b Time duration for different staining agents.

6.3a Hedonic scale for sensory evaluation of Moringa leaves ODTs.
6.3b  Detail of quotations received from different suppliers  

6.4a  Cost of raw materials for 1.5 million MODT.  

6.4b  Operational cost and salaries of labor working at the pharmaceutical industry.  

6.5  Prices and descriptions of synthetic multivitamins available in the Malaysian market.  

6.6  Nutritional facts of optimum (F9) MODTs and RDA of adolescence.
# LIST OF FIGURES

<table>
<thead>
<tr>
<th>Figure</th>
<th>Description</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.1</td>
<td>A 10 years (approximately) old <em>Moringa oleifera</em> trees planted at Universiti Putra Malaysia, Serdang, Selangor, Malaysia.</td>
<td>1</td>
</tr>
<tr>
<td>1.2</td>
<td>Natural growing of Moringa tree (green) and malnutrition (red) regions in World map (Anonymous, 2015a).</td>
<td>2</td>
</tr>
<tr>
<td>1.3</td>
<td>Flow chart for the plan of study</td>
<td>10</td>
</tr>
<tr>
<td>2.2</td>
<td><em>Moringa oleifera</em> leave’s products available in global market.</td>
<td>14</td>
</tr>
<tr>
<td>2.3</td>
<td>Overall drying process (Mercer, 2007).</td>
<td>18</td>
</tr>
<tr>
<td>3.1</td>
<td>Flow chart for drying of Moringa leaves and banana fruit.</td>
<td>44</td>
</tr>
<tr>
<td>3.2</td>
<td>Final moisture content (w.b) and drying time of different drying treatments.</td>
<td>55</td>
</tr>
<tr>
<td>3.3</td>
<td>Drying rate as a function of drying time of different drying treatments.</td>
<td>55</td>
</tr>
<tr>
<td>3.4</td>
<td>Difference in moisture ratio as a function of drying time of different drying treatments.</td>
<td>56</td>
</tr>
<tr>
<td>3.5</td>
<td>Constants of Page’s model with different drying treatments.</td>
<td>57</td>
</tr>
<tr>
<td>3.6</td>
<td>Actual and predicted curve plots of all drying treatments with Page’s model.</td>
<td>59</td>
</tr>
<tr>
<td>3.7</td>
<td>The original photographs of fresh and dried Moringa leaves.</td>
<td>60</td>
</tr>
<tr>
<td>3.8</td>
<td>Colour analysis of Moringa leaves with respect to drying treatments.</td>
<td>61</td>
</tr>
<tr>
<td>3.9</td>
<td>Time taken to reach final moisture level (w.b) of different banana slice thickness and at different oven temperatures.</td>
<td>64</td>
</tr>
</tbody>
</table>
3.10a Water removal rate of 4 mm banana slices at different oven drying temperatures.

3.10b Water removal rate of 7 mm banana slices at different oven drying temperatures.

3.10c Water removal rate of 10 mm banana slices at different oven drying temperatures.

3.11 Effect of oven drying temperatures on colour of banana slices (4 mm).

3.12 Effect of drying temperatures on colour of banana slices.

3.13 Banana powder prepared from banana slices dried at 70 °C.

4.1 Flow chart of Processing of Moringa leaves and excipients.

4.2 Cutter mill (SM 200, Retsch, Germany).

4.3 Hammer mill (Perten-120, Perten Instruments AB, Sweden).

4.4 Dry mill (HR2021/70 Philips, Netherland).

4.5 A 13 mm stainless steel die and universal compaction machine (Instron 5566, Canton, MA).

4.6 Experimental setup for measuring the tensile strength of tablets.

4.7 SEM images (300 X) of Moringa leaves particles prepared with a) dry mill b) hammer mill and c) cutter mill.

4.8a Effect of moisture content and particles size and shape on Carr Index of Moringa leaves powder.

4.8b Response surface plot showing effect of moisture and particles size of Moringa leaves powder on Carr Index.

4.9a Effect of moisture content, particles shape and size on Cohesion Index (Col) of Moringa leaves powder.
4.9b Response surface plot showing the effect of moisture and particles size of Moringa leaves powder on Cohesion Index.

4.10a Effect of moisture content, particles shape and size on the mean caking strength of Moringa leaves powder.

4.10b Response surface plot showing the effect of moisture and particles size of Moringa leaves powder on the mean caking strength.

4.11 Curve plot generated by Exponent software during cohesion test of Moringa leaves powder.

4.12 Curve plot generated by Exponent software during caking test of Moringa leaves powder.

4.13 Curve plot generated by Exponent software during PFSD test of Moringa leaves powder.

4.14a Linear relationship between $P$ and $P/C$ of Kawakita and Lüdè’s equation.

4.14b Linear relationship between $P$ and $\ln[1/(1-D)]$ of Heckel’s equation.

4.14c Linear relationship between $\ln(P)$ and strain ($\varepsilon$) of Adam’s equation.

4.14d Linear relationship between $P^{1/2}$ and $\ln[1/(1-D)]$ of Panelli-Filho’s equation.

4.15 Tablets prepared from pure excipients a) Banana, b) MCC, c) Moringa and d) AcDiSol.

4.16 Tensile strength of excipients used in MODTs.

5.1 Flow chart of development of MODTs.

5.2 Simplex Lattice Design for three components

5.3 Wetting pattern of MODT placed on a wet tissue paper.

5.4 Disintegration mechanism of MODT in water.

5.5 Disintegration time and dissolution rate setup of MODTs.
5.6 CI with banana.  
5.7 CI with AcDiSol.  
5.8 HR with banana.  
5.9 HR with AcDiSol.  
5.10 CoI with banana.  
5.11 CoI with AcDiSol.  
5.12 Linear relationship between $P$ and $P/C$ of Kawakita and Lüdde’s equation.  
5.13 Linear relationship between $P$ and $\ln[1/(1-D)]$ of Heckel’s equation.  
5.14 Linear relationship between $\ln(P)$ and strain ($\varepsilon$) of Adam’s equation.  
5.15 Linear relationship between $P^{1/2}$ and $\ln[1/(1-D)]$ of Panelli-Filho’s equation.  
5.16 Effect of concentrations of banana (A), MCC (B) and mannitol (C) on hardness of MODTs.  
5.17 Effect of concentrations of AcDiSol (A), MCC (B) and mannitol (C) on hardness of MODTs.  
5.18 Tensile strength of formulated mixtures (F1-F10) of MODTs (banana powder).  
5.19 Tensile strength of formulated mixtures (F1-F10) of MODTs (AcDiSol).  
5.20 Effect of concentrations of banana (A), MCC (B) and mannitol (C) on friability (%) of MODTs.  
5.21 Effect of concentrations of AcDiSol (A), MCC (B) and mannitol (C) on friability (%) of MODTs.  
5.22 Effect of concentrations of banana (A), MCC (B) and mannitol (C) on disintegration time (s) of MODTs.
5.23 Effect of concentrations of AcDiSol (A), MCC (B) and mannitol (C) on disintegration time (s) of MODTs.

5.24 Effect of concentrations of banana (A), MCC (B) and mannitol (C) on wetting time (s) of MODTs.

5.25 Effect of concentrations of AcDiSol (A), MCC (B) and mannitol (C) on wetting time (s) of MODTs.

5.26 Cumulative dissolution versus time curves of MODTs in distilled water with banana powder as superdisintegrant.

5.27 Cumulative dissolution versus time curves of MODTs in distilled water with AcDiSol as superdisintegrant.

5.28 Cumulative dissolution versus time curves of MODTs in simulated saliva water with banana powder as superdisintegrant.

5.29 Cumulative dissolution versus time curves of MODTs in simulated saliva with AcDiSol as superdisintegrant.

6.1 Flow chart of stability, biological and economical studies of MODTs.

6.2 Effect of dosage rates on the growth of rabbits.

6.3a Kidney medulla section of placebo (left) and treated with highest dosage rate of 250 mg/kg body weight (right) rabbit.

6.3b Liver (central vein) section of placebo (left) and treated with highest dosage rate of 250 mg/kg body weight (right) rabbit.

6.4a Hardness change of optimum MODT with respect to time under normal and accelerated conditions.

6.4b Weight change of optimum MODT with respect to time under normal and accelerated conditions.

6.4c Disintegration time change of optimum MODT with respect to time under normal and accelerated conditions.

6.5 Final form of optimum MODTs.
## LIST OF APPENDICES

<table>
<thead>
<tr>
<th>Appendix</th>
<th>Description</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>A1</td>
<td>Colour coordinate values of fresh and dried Moringa leaves.</td>
<td>188</td>
</tr>
<tr>
<td>A2</td>
<td>Colour coordinates values of fresh and dried banana slices.</td>
<td>188</td>
</tr>
<tr>
<td>A3-a</td>
<td>Bulk and tapped densities measuring setup.</td>
<td>189</td>
</tr>
<tr>
<td>A3-b</td>
<td>Particles size distribution report of banana powder generated by Mastersizeer 2000 software.</td>
<td>191</td>
</tr>
<tr>
<td>A4</td>
<td>A texture analyser equipped with powder flow analyser during caking test.</td>
<td>191</td>
</tr>
<tr>
<td>A5-a</td>
<td>Co-relation between Carr Index (CI) and Cohesion Index (CoI).</td>
<td>192</td>
</tr>
<tr>
<td>A5-b</td>
<td>Co-relation between Carr Index (CI) and mean caking strength (MCS).</td>
<td>192</td>
</tr>
<tr>
<td>A5-c</td>
<td>Co-relation between Cohesion Index (CoI) and mean caking strength (MCS).</td>
<td>193</td>
</tr>
<tr>
<td>A6-a</td>
<td>Cohesion Index (CoI) curve plot of AcDiSol.</td>
<td>194</td>
</tr>
<tr>
<td>A6-b</td>
<td>Cohesion Index (CoI) curve plot of banana powder.</td>
<td>194</td>
</tr>
<tr>
<td>A7-a</td>
<td>Physical properties of formulated (F1-F10) mixtures with banana powder as superdisintegrant.</td>
<td>195</td>
</tr>
<tr>
<td>A7-b</td>
<td>Physical properties of formulated (F1-F10) mixtures with AcDiSol as superdisintegrant.</td>
<td>196</td>
</tr>
<tr>
<td>A7-c</td>
<td>Flow properties of formulated (F1-F10) mixtures with banana powder as superdisintegrant.</td>
<td>197</td>
</tr>
<tr>
<td>A7-d</td>
<td>Flow properties of formulated (F1-F10) mixtures with AcDiSol as superdisintegrant.</td>
<td>198</td>
</tr>
<tr>
<td>A8</td>
<td>Statistical analysis of dissolution profile of MODTs prepared with banana powder in distilled water.</td>
<td>199</td>
</tr>
</tbody>
</table>
A9 Statistical analysis of dissolution profile of MODTs prepared with AcDiSol in distilled water.

A10 Statistical analysis of dissolution profile of MODTs prepared with banana powder in simulated saliva.

A11 Statistical analysis of dissolution profile of MODTs prepared with AcDiSol in simulated saliva.

A12 $f_2$ values of F9 (reference) with formulations (F1-F8 and F10) of MODTs with banana in distilled water.

A13 $f_2$ values of F9 (reference) with formulations (F1-F8 and F10) of MODTs with banana powder in simulated saliva.

A14 $f_2$ values of F9 (reference) with formulations (F1-F8 and F10) of MODTs with AcDiSol in distilled water.

A15 $f_2$ values of F9 (reference) with formulations (F1-F8 and F10) of MODTs with AcDiSol in simulated saliva.

A16 $f_1$ values of F9 (reference) with formulations (F1-F8 and F10) of MODTs with banana in distilled water.

A17 $f_1$ values of F9 (reference) with formulations (F1-F8 and F10) of MODTs with banana powder in simulated saliva.

A18 $f_1$ values of F9 (reference) with formulations (F1-F8 and F10) of MODTs with AcDiSol in distilled water.

A19 $f_1$ values of F9 (reference) with formulations (F1-F8 and F10) of MODTs with AcDiSol in simulated saliva.

A20 Different groups of rabbits during biological trials.

A21 Rabbits growth rate assessment at Department of Pharmacology, University of Agriculture, Faisalabad, Pakistan.

A22 Permission letter scanned copy issued by Department of Pharmacology, University of Agriculture, Faisalabad, Pakistan.
LIST OF ABBREVIATIONS

<table>
<thead>
<tr>
<th>Symbol</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>µL</td>
<td>Micro Liter</td>
</tr>
<tr>
<td>µm</td>
<td>Micrometer</td>
</tr>
<tr>
<td>AIC</td>
<td>Akaike Information Criterion</td>
</tr>
<tr>
<td>ALT</td>
<td>Alanine Aminotransferase</td>
</tr>
<tr>
<td>API</td>
<td>Active Pharmaceutical Ingredient</td>
</tr>
<tr>
<td>ASAE</td>
<td>American Society of Associate Executives</td>
</tr>
<tr>
<td>AST</td>
<td>Aspartate Aminotransferase</td>
</tr>
<tr>
<td>BGL</td>
<td>Blood Glucose Level</td>
</tr>
<tr>
<td>CI</td>
<td>Carr Index</td>
</tr>
<tr>
<td>CDER</td>
<td>Center for Drug Evaluation and Research</td>
</tr>
<tr>
<td>CIE</td>
<td>International Commission on Illumination</td>
</tr>
<tr>
<td>CoI</td>
<td>Cohesion Index</td>
</tr>
<tr>
<td>D_{50}</td>
<td>Median Diameter</td>
</tr>
<tr>
<td>DNA</td>
<td>Deoxyribonucleic Acid</td>
</tr>
<tr>
<td>DoE</td>
<td>Design of Expert</td>
</tr>
<tr>
<td>DPX</td>
<td>Dibutyl Phthalate and Xylene</td>
</tr>
<tr>
<td>DR</td>
<td>Drying Rate</td>
</tr>
<tr>
<td>DT</td>
<td>Drying Time</td>
</tr>
<tr>
<td>EUP</td>
<td>European Pharmacopoeia</td>
</tr>
<tr>
<td>FBS</td>
<td>Fasting Blood Sugar</td>
</tr>
<tr>
<td>FDA</td>
<td>Food and Drug Administration</td>
</tr>
<tr>
<td>FAD</td>
<td>Flavin Adenine Dinucleotide</td>
</tr>
<tr>
<td>FMN</td>
<td>Flavin Mononucleotide</td>
</tr>
<tr>
<td>FSR</td>
<td>Force-Sensitive Resistor</td>
</tr>
<tr>
<td>HR</td>
<td>Hausner Ratio</td>
</tr>
<tr>
<td>HCl</td>
<td>Hydrochloric acid</td>
</tr>
<tr>
<td>HDRA</td>
<td>Henry Doubleday Research Association</td>
</tr>
<tr>
<td>HIV</td>
<td>Human Immune Deficiency Virus</td>
</tr>
<tr>
<td>HPLC</td>
<td>High Performance Liquid Chromatography</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Description</td>
</tr>
<tr>
<td>--------------</td>
<td>-------------</td>
</tr>
<tr>
<td>IDRG</td>
<td>International Development Resource Group</td>
</tr>
<tr>
<td>kN</td>
<td>Kilo Newton</td>
</tr>
<tr>
<td>LCD</td>
<td>Liquid Crystal Display</td>
</tr>
<tr>
<td>LD&lt;sub&gt;50&lt;/sub&gt;</td>
<td>Lethal Dose</td>
</tr>
<tr>
<td>MCC</td>
<td>Microcrystalline Cellulose</td>
</tr>
<tr>
<td>mg</td>
<td>Milligram</td>
</tr>
<tr>
<td>mL</td>
<td>Milliliter</td>
</tr>
<tr>
<td>MLP</td>
<td>Moringa Leaves Powder</td>
</tr>
<tr>
<td>MODT&lt;sub&gt;s&lt;/sub&gt;</td>
<td>Moringa Orally Disintegrating Tablets</td>
</tr>
<tr>
<td>MPa</td>
<td>Mega Pascal</td>
</tr>
<tr>
<td>MR</td>
<td>Moisture Ratio</td>
</tr>
<tr>
<td>ODT&lt;sub&gt;s&lt;/sub&gt;</td>
<td>Orally Disintegrating Tablets</td>
</tr>
<tr>
<td>OGTT</td>
<td>Oral Glucose Tolerance Test</td>
</tr>
<tr>
<td>PFA</td>
<td>Powder Flow Analyser</td>
</tr>
<tr>
<td>psi</td>
<td>Pounds Per Square Inch</td>
</tr>
<tr>
<td>R&lt;sup&gt;2&lt;/sup&gt;</td>
<td>Coefficient of Determination</td>
</tr>
<tr>
<td>RBS</td>
<td>Random Blood Sugar</td>
</tr>
<tr>
<td>RDA</td>
<td>Recommended Dietary Allowance</td>
</tr>
<tr>
<td>RM</td>
<td>Malaysian Ringgit</td>
</tr>
<tr>
<td>rpm</td>
<td>Revolution per minute</td>
</tr>
<tr>
<td>RMSE</td>
<td>Root Mean Square Error</td>
</tr>
<tr>
<td>sec</td>
<td>Seconds</td>
</tr>
<tr>
<td>UDU</td>
<td>Uniformity of Dosage Unit</td>
</tr>
<tr>
<td>USD</td>
<td>United State Dollar</td>
</tr>
<tr>
<td>UV</td>
<td>Ultra violet</td>
</tr>
<tr>
<td>X&lt;sup&gt;2&lt;/sup&gt;</td>
<td>Reduced Chi Square</td>
</tr>
</tbody>
</table>
CHAPTER 1

INTRODUCTION

1.1 *Moringa Oleifera* Tree

The *Moringa oleifera* Lam. tree (Figure 1.1) commonly referred as drumstick tree, miracle tree, tree for life and mother’s best friend (Gopalakrishnan *et al.*, 2016) is a plant from the Moringaceae family.

![Figure 1.1 : A 10 years (approximately) old *Moringa oleifera* trees planted at Universiti Putra Malaysia, Serdang, Selangor, Malaysia.](image)
It is native to Pakistan and India and naturalised tropic and sub-tropic regions of the World as shown in Figure 1.2. As the pods are shaped like drum sticks, it is also called drumstick tree. Its roots taste like horseradish, hence also called horseradish tree (Little and Wadsworth, 1964; Morton, 1991). Moringa is a small, fast-growing evergreen tree that usually grows up to 8-10 m in height (Fuglie, 2005). It is a fast growing tree that usually grows up to 10 m height, with grey thick bark and a thin crown. The tree requires an average annual rainfall ranging between 250-3000 mm and survives in a temperature range of 25 to 40 °C which makes it suitable for tropical regions (HDRA, 2002; Ramachandran et al., 1980). Moringa has different names in different languages like Lemunggai or Murungai in Malay, Sohanjna in Urdu, Sahijna in Hindi, Maranga calalu in Spanish, Horseradish tree in English, Kelor in Bali, Kaanaeng-doeng in Thai and Saisam in Arabic. It has valued mainly for its edible fruits, flowers, roots, seeds and most importantly leaves in traditional medicine throughout its native and introduced (Figure 1.2) ranges (Lim, 2012). The leaves of Moringa are green in colour and elliptical in shape about 1-2 cm in length (Sharma and Pracheta, 2011). Moreover, being a good source of multivitamins, micro-macro minerals, antioxidants, fatty acids, phenolics and all essential amino acids Moringa leaves have been used in traditional medicines for centuries (Anwar et al., 2007; Fahey, 2005). Moringa leaves also have medicinal properties and various studies conducted on their medicinal usage such as being antioxidant, anticancer, antiviral, cardio-protective, anti-inflammatory, anti-asthmatic and others (Lim, 2012).
1.1.1 Nutritional Facts of Moringa Leaves

Scientists who are doing research on Moringa tree reported that Moringa leaves have potential to save the lives of millions of people on our planet as it was estimated that almost 300 diseases can be treated with different parts of Moringa tree. Moringa leaves contain almost 90 nutrients, 18 amino acids and different antioxidants (Fuglie, 2005). There are many claims regarding nutritional facts of dried Moringa leaves, such as 17 times more calcium than cow’s milk, 8.8 times more iron than fillet beef, 14 times more potassium than banana, 8 times more vitamin A than carrot and ½ times vitamin C than orange (Barta, 2011; Fuglie, 2005). There was wide variation in data related to nutrient contents of Moringa leaves. This variation in data was due to agro-climatic conditions, analytical methodology, different stages of leaves maturity and drying method (Makkar and Becker, 1996). So, maximum and minimum range of all nutrients reported in the literature were reviewed and listed in Table 1.1. In the case of vitamins there is only a single source available in which researcher used only shade drying treatment to dry African ecotype Moringa leaves.
Table 1.1: Nutrients range of Moringa leaves reported in different studies.

<table>
<thead>
<tr>
<th>Nutrients</th>
<th>Units</th>
<th>Value (Range)</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Protein</td>
<td>g/100g</td>
<td>16-32</td>
<td>Arbeit (2013)</td>
</tr>
<tr>
<td>Carbohydrates</td>
<td>g/100g</td>
<td>28-45</td>
<td></td>
</tr>
<tr>
<td>Fat</td>
<td>g/100g</td>
<td>9-22</td>
<td>Moyo et al. (2011)</td>
</tr>
<tr>
<td>Calcium</td>
<td>mg/100g</td>
<td>1088-3512</td>
<td>Yameogo et al. (2011)</td>
</tr>
<tr>
<td>Potassium</td>
<td>mg/100g</td>
<td>1120-2290</td>
<td>Offor et al. (2014)</td>
</tr>
<tr>
<td>Iron</td>
<td>mg/100g</td>
<td>33.5-57.6</td>
<td>Mbah et al. (2012)</td>
</tr>
<tr>
<td>Copper</td>
<td>mg/100g</td>
<td>0.8-0.9</td>
<td>Asante et al. (2014)</td>
</tr>
<tr>
<td>Zinc</td>
<td>mg/100g</td>
<td>4.0-6.1</td>
<td>Satwase et al. (2013)</td>
</tr>
<tr>
<td>β-carotene</td>
<td>mg/100g</td>
<td>16.3</td>
<td>Joshi and Mehta (2010)</td>
</tr>
<tr>
<td>Thiamine</td>
<td>mg/100g</td>
<td>2.64</td>
<td>Olagbemide and Alikwe (2014)</td>
</tr>
<tr>
<td>Riboflavin</td>
<td>mg/100g</td>
<td>20.5</td>
<td>Price (2007)</td>
</tr>
<tr>
<td>Niacin</td>
<td>mg/100g</td>
<td>8.2</td>
<td></td>
</tr>
<tr>
<td>Ascorbic acid</td>
<td>mg/100g</td>
<td>17.3</td>
<td></td>
</tr>
<tr>
<td>α-tocopherol</td>
<td>mg/100g</td>
<td>113</td>
<td></td>
</tr>
<tr>
<td>Histidine</td>
<td>g/100g</td>
<td>0.39-1.90</td>
<td></td>
</tr>
<tr>
<td>Isoleucine</td>
<td>g/100g</td>
<td>0.78-2.33</td>
<td></td>
</tr>
<tr>
<td>Leucine</td>
<td>g/100g</td>
<td>1.55-3.60</td>
<td></td>
</tr>
<tr>
<td>Lysine</td>
<td>g/100g</td>
<td>0.95-1.64</td>
<td></td>
</tr>
<tr>
<td>Methionine</td>
<td>g/100g</td>
<td>0.23-0.95</td>
<td></td>
</tr>
<tr>
<td>Phenylalanine</td>
<td>g/100g</td>
<td>1.05-4.26</td>
<td></td>
</tr>
<tr>
<td>Threonine</td>
<td>g/100g</td>
<td>0.71-4.38</td>
<td></td>
</tr>
<tr>
<td>Tryptophan</td>
<td>g/100g</td>
<td>0.43-0.75</td>
<td></td>
</tr>
<tr>
<td>Valine</td>
<td>g/100g</td>
<td>1.06-3.36</td>
<td></td>
</tr>
</tbody>
</table>
1.2 Processing of Leaves

1.2.1 Drying of Leaves

For the preservation of food items, drying is one of the oldest and widely used methods all over the World. Drying results in altering food properties including colour, aroma, texture, nutritional value and physical appearance. Conditions of drying have a great influence on quality attributes of the dried product. High drying temperature reduces the drying time, but at the same time compromises the quality of the product, may damage the surface and consumes a higher amount of energy. On the other hand, mild drying conditions using lower ranges of temperature may result in improved quality of the product, but reduces the drying rate thus drying period is prolonged (Kumar et al., 2014). There are different conventional and advanced drying techniques being used in field and industry. Conventional methods such as shade, sun and oven drying are used in developing countries. However, advanced methods like microwave and freeze, vacuum and spray drying are commonly used in developed countries. Each method has its own advantages and disadvantages as shade drying at room temperature can conserve nutrients but leads to contamination from surrounding environment such as dust particles, insects and rodents. In sun drying, duration of exposure is less but ultra violet radiations cause destruction of nutrients. The oven drying method is used as standard laboratory method to determine the effect of varying temperatures on product quality in terms of nutrient. Microwave drying is used for rapid drying but very high temperature may burn the heat labile nutrients. Freeze and spray dryings are the advanced methods and nowadays commonly used in industries for heat sensitive food products. Freeze drying method considered to the lowest nutrients loss but it is a very expensive method which limits its applications. While, in spray drying, dry powder is obtained from a liquid composition which changes the biochemistry of product.

1.2.2 Powder Formation

After drying, powder formation is the next step in food processing and pharmaceutical industries. Powder formation mechanisms such as dry, hammer and cutter mills commonly used in food industry. Particle size and particle shape are important physical properties of food powders as they have an effect on product performance, bulk properties, flowability, stability, compactability, dissolution and appearance of the end product. Very fine particles having poor flowability can create problems during handling and storage of pharmaceutical powders but having high dissolution rate and vice versa. The flowability of powders can be characterised according to Carr Index (Carr, 1965), Hausner Ratio (Hausner, 1967), Angle of Repose and Cohesion Index (PFA, 2015).
1.2.3 Tablet Formulation and Evaluation

Over the past few decades, orally disintegrating tablets (ODTs) have gained much consideration as an ideal substitute to conventional oral dosage forms such as capsules and tablets. The United State Food and Drug Administration Center for Drug Evaluation and Research (CDER) defines the ODT as a solid dosage form containing medicinal substances, which disintegrates rapidly, usually within a matter of seconds, when placed upon the tongue (FDA, 2009). The European Pharmacopoeia however, defines a similar term, orodisperse, as a tablet that can be placed in the mouth where it disperses rapidly before swallowing (Sastry et al., 2000). Recent market studies indicate that more than half of the patient population prefers ODTs to other dosage forms and most consumers would ask their doctors for ODTs (Brown, 2003). These responses may, in part, be attributed to knowing ODT advantages such as ease of administration, ease of swallowing, pleasant taste, and the availability of several flavours (Behnke et al., 2003). Orally disintegrating tablets offer all the advantages of conventional dosage form (capsules and tablets) along with following special considerations which include;

i) As ODT is unit solid dosage form which provides easy manufacturing, small packaging size, better compliance, good stability and precise dosing (Seager, 1998; Habib et al., 2000; Brown, 2003).

ii) There is no threat of obstruction of this dosage form, which is favorable for travelling patients who may not have access to water.

iii) Easy to administer in children, elderly, and institutionalised patients (especially psychiatric and mentally retarded patient). Rapid disintegration of the tablet is followed by its fast dissolution and prompt absorption which provide quick onset of action (Badgujar and Mundada, 2011; Dobetti, 2003). In addition, rapid disintegration of tablets may cause rapid dissolution and absorption and thus may cause the medicine to show its effect rapidly (Behnke et al., 2003).

iv) Flavours and sweeteners in ODTs change the bitter pills into good mouth feel.

v) Orally disintegrating tablets are preferred especially by children and elderly people as well as the patients who wish to take their medicine at any time comfortably (Sastry et al., 2000; Bandari et al., 2008).

vi) Absorption of the tablet in mouth avoids liver metabolism, which reduces the dose and increases the amount of active drug in the body (Clarke et al., 2003).
Although Moringa leaves are available in the form of Moringa tea and conventional dosage in some countries but most of the heat labile vitamins (water soluble vitamins) are evaporated at high temperature (Akah and Onweluzo, 2014) of water in case of Moringa tea. Conventional dosage (oral tablet and capsule) undergo a large first pass effect (gastric absorption and liver metabolism). Drug dissolution and absorption, as well as the onset of clinical effect and drug bioavailability (concentration of active drug in the blood) of ODTs may be significantly greater than those observed from conventional dosage forms.

1.3 Problem Statement and Objectives

Herbs and leaves of medicinal plants contain rich amount of nutrients and are being used to cure many diseases from centuries. According to World Health Organization, approximately two-thirds of World’s population today still relies on herbal medication as component of their primary healthcare (WHO, 2010). After the invention of pharmaceutical dosages like a tablet, capsules and other forms, the use of herbs and medicinal plant leaves in their pure form became limited due to inadequate information about the composition of constituents, inaccurate dosage rate, the toxic effect of pesticides, and conventional drying techniques. Herbal based medications need a scientific evaluation of their pharmacological standards and safety that can be determined using pharmacogenomics technology. With increasing tendencies for the use of naturally derived substances throughout the world, there is a need to conduct pragmatic and explanatory studies considering complementary for acquiring a reliable data for health caregiver as well as for the patient and not to believe in millenarian beliefs and myths. While herbal medicine can potentially contribute to the advancement of healthcare, many major challenges must be overcome prior to the successful integration of herbal medication remedies into mainstream medicine.

Fresh Moringa leaves contained 75% moisture content which make them highly pericable. After drying the taste of Moringa leaves become extremely bitter which is very difficult to swallow. If convert these dried leaves into powder form for further processing like convert into tablet. Powder shows high cohesion and caking strength. Due to low bulk density the nature of powder is very lose and fluffy which make it difficult to process in tablet forming and capsule filling machines because good flowability of powders is the basic requirement of tableting manufacturing process. The hardness and tensile strength of tablets made by Moringa leaves powder also have very less due to which tablets are not very stable during handling and shipping processes. In addition, Moringa leaves also have very poor dissolution in liquid mediums due to very low bulk density, the particles are flot on the surface of liquid medium rather dissolve. The above mentioned problems
are not only associated with only Moringa leaves powder these a very common with all other herbal powders. Therefore, the aim of present study is find a solution which can overcome all above mentioned problems in an economical way.

Additionally, to establish credibility for herbal use in the modern settings, scientific-based studies must be transformed into evidence-based claims. Once these issues are resolved, the prospect exists for the widespread use of herbal medicine as a safe, effective, and affordable form of healthcare.

Therefore, a comprehensive study was planned to introduce herbs and medicinal plant leaves in a more accurate, safe, effective, affordable and readily available form which can compete and fulfill standard parameters described by Food and Drug Administration (FDA) and The International Pharmacopoeia (Ph. Int.) for pharmaceutical dosages. In this purpose, *Moringa oleifera* leaves were selected and effort was made to convert these precious leaves into readily available, acceptable and affordable for all age group of peoples without changing their chemistry (in pure form) such as orally disintegrating tablets.

Therefore, the present study was planned to investigate the use of *Moringa oleifera* leaves in a readily available that is acceptable and affordable to all regions and age groups of people such as tablets (Orally Disintegrating Tablets), in terms of raising the missing vitamins levels.

The objectives of study are:

i) To determine the drying behaviour, colour quality and nutritional facts of *Moringa oleifera* leaves and banana slices with different drying treatments.

ii) To evaluate the physical (densities, particles size and shape) and flow (cohesion index and mean caking strength) properties of whole Moringa leaves powder and excipients used in the formulation of Moringa orally disintegrating tablets.

iii) To develop, formulate and evaluate the Moringa orally disintegrating tablets by direct compression method using different concentrations of diluent, superdisintegrant and sweetener to meet standard parameters.

iv) To assess the feasibility, stability and toxicological effects of optimum formulated Moringa orally disintegrating tablets.
1.4 Scope of Study

This study focuses on tableting of Moringa leaves according to the standard parameters described by FDA and International Pharmacopeia for orally disintegrating tablets. The fresh Moringa leaves contained 75% moisture content and bitter in taste. The taste of these leaves become extremely bitter after drying and many vitamins were also lost during conventional (shade and sunlight) drying methods. The powder of Moringa leaves also shown poor flowability which make it difficult to convert into tablet in pure form.

The scope of present research work is illustrated in Figure 1.3.

1.5 Research Hypothesis

After reviewing the problems related to processing of herbal and medicinal plant leaves in previous literature, the following hypotheses are established.

i) The standardisation of herbal and medicinal plant leaves powder can be done according to the parameters described by FDA and International Pharmacopeia.

ii) Banana powder has the abilities to act as natural superdisintegrant like other synthetic superdisintegrants.
Figure 1.3: Flow chart for the plan of study.
1.6 Outline of the Thesis

Chapter 1 A comprehensive introduction of *Moringa oleifera* tree, its usage and nutritional facts. Different drying technologies used for leaves drying, conventional and advanced physical and flow properties determination techniques, orally disintegrating tablets advantages and tablet evaluation was given in this chapter. End of this chapter clearly states the problem statement, objectives, hypothesis and plan of study along with an outline of the thesis.

Chapter 2 Detailed literature is discussed in this chapter in order to obtain sufficient information for experimental design. The drying technologies for leaves, powder flow properties with one of the advanced tool; powder flow analyser, excipients used in the formulation of orally disintegrating tablets, standard parameters for the evaluation of orally disintegrating tablets and biological studies of a drug were reviewed in detail.

Chapter 3 Presented the details of materials and methods used in drying, empirical modelling, colour analysis and vitamins analysis of fresh and dried Moringa leaves and banana slices. This chapter also concluded the optimum drying treatments for Moringa leaves and banana slices in terms of colour quality and vitamins preservation.

Chapter 4 Presented the different grinding mechanisms in investigating the effect of particles shape on the flowability of powders. Conventional and advanced methods for measuring physical and flow properties of powders were employed. A correlation between conventional and advanced methods of the flowability measurement was also presented in this chapter. This chapter also disclosed the compaction behaviour using mathematical modelling of whole Moringa leaves powder and all excipients used in the formulation.

Chapter 5 Explained the direct compression method to make Moringa leaves orally disintegrating tablets and also reported the methodology of tablet evaluation on the basis of parameters set by Food and Drug Administration. The Design of Expert 8.0 ® (DoE) software was used to formulate different excipients at a minimum and maximum level. In this chapter the pre and post compression behaviour of formulated mixtures were determined using standard flowability scales (Carr Index and Cohesion Index) and mathematical modelling. The evaluation of formulated tablets was made according to the standards of Food and Drug Administration and International Pharmacopoeia for orally disintegrating tablets.
Chapter 6 Determined the stability of optimum formulated Moringa leaves ODTs. The toxic effect of optimum MODT on liver and kidney cells of rabbits, the economic feasibility and final nutritional facts of the optimum tablets in terms of percent recommended daily allowance were examined.

Chapter 7 A brief conclusion, a summary of experimental results, and future recommendations are stated in this chapter.
REFERENCES


Anonymous 2016b. http://miracletrees.org/Pflügerstr 63, 12043 Berlin, Germany. 22 Shelter Rock Lane Unit 3 Danbury CT 06810, Connecticut, USA (Downloaded. 07.08.2016).


FMC Biopolymer, 2009. Ac-Di-Sol(R) and Avicel PH101 are the trademarks of FMC Corporation. http://www.fmcbiopolymer.com/Pharmaceutical/Products/AcDiSol.aspx (Downloaded. 20.04.2015).


Fuglie, L.J. 2005. The Moringa Tree: A local solution to malnutrition *ChurchWorld Service in Senegal*. 

171


containing corn, sweet potato, and cocoyam starches as binders. *Pharma Technology* 29: 82-90.


