

THESIS

A STUDY ON THE COMBINATION OF MCC- PGS AND MCC-PVP AS CUSHIONING AGENTS IN MUPS TABLET



NG CHEE XUAN

**FACULTY OF PHARMACY UNIVERSITAS AIRLANGGA
DEPARTEMEN ILMU KEFARMASIAN
SURABAYA
2022**

THESIS

A STUDY ON THE COMBINATION OF MCC- PGS AND MCC-PVP AS CUSHIONING AGENTS IN MUPS TABLET



NG CHEE XUAN

**FACULTY OF PHARMACY UNIVERSITAS AIRLANGGA
DEPARTEMEN ILMU KEFARMASIAN
SURABAYA**

2022

APPROVAL SHEET

**A STUDY ON THE COMBINATION OF MCC-PGS
AND MCC-PVP AS CUSHIONING AGENTS
IN MUPS TABLET**

THESIS

Submitted In Partial Fulfilment Of The Requirement

For The Bachelor Of Pharmacy At

Faculty Of Pharmacy Universitas Airlangga

2022

By:

Ng Chee Xuan

NIM: 051811133245

Approval of Supervising Committee

on 5 August 2022:

Supervisor



Dr. rer. nat. Maria L. A. D. Lestari, Apt.

NIP. 198004262005012004

Co-supervisor



apt. Dini Retnowati, M.Si.

NIP. 198507192008122003

SURAT PERNYATAAN

Yang bertanda tangan di bawah ini,

Nama : Ng Chee Xuan

NIM : 051811133245

adalah mahasiswa Fakultas Farmasi, Universitas Airlangga, menyatakan dengan sesungguhnya bahwa Naskah Tugas Akhir/Skripsi yang saya tulis dengan judul:

A Study On The Combination Of MCC-PGS And MCC-PVP As Cushioning Agents In MUPS Tablet

adalah benar-benar merupakan hasil karya saya sendiri. Apabila di kemudian hari diketahui bahwa isi Naskah Skripsi ini merupakan hasil plagiasi, maka saya bersedia menerima sanksi berupa pembatalan kelulusan dan atau pencabutan gelar yang saya peroleh.

Demikian surat pernyataan ini saya buat untuk dapat dipergunakan sebagaimana mestinya.

Surabaya, 20 Juli 2022

Yang membuat pernyataan,



Ng Chee Xuan

NIM 051811133245

SURAT PERNYATAAN

Yang bertanda tangan di bawah ini,

Nama : Ng Chee Xuan

NIM : 051811133245

menyatakan bahwa demi kepentingan perkembangan ilmu pengetahuan, saya menyetujui abstrak Skripsi yang saya tulis dengan judul:

A Study On The Combination Of MCC-PGS And MCC-PVP As Cushioning Agents In MUPS Tablet

untuk dipublikasikan atau ditampilkan di internet atau media lain yaitu Digital Library Perpustakaan Universitas Airlangga untuk kepentingan akademik, sebatas sesuai dengan Undang-Undang Hak Cipta.

Demikian surat pernyataan ini saya buat untuk dapat dipergunakan sebagaimana mestinya.

Surabaya, 20 Juli 2022

Yang membuat pernyataan,



Ng Chee Xuan

NIM 051811133245

ACKNOWLEDGEMENT

All praises to God for the strength He showered on the author to complete this thesis entitled **A Study On The Combination of MCC-PGS And MCC-PVP As Cushioning Agents In MUPS Tablet**. The author would like to express profound gratitude to all the individuals mentioned below:

1. Dr.rer.nat. Maria L.A.D. Lestari, Apt as the supervisor for believing in the author, for her valuable suggestions, and for timely help. Grateful acknowledgment of all the sincere attitudes and patience that make each day counts throughout this thesis.
2. apt. Dini Retnowati., S. Farm., M.Si. as the co-supervisor, for support, encouragement, motivation, and guidance to the author in completing the thesis.
All in all, it has been a pleasure and an honor to have them as the author's supervisors.
3. Prof. Dr. Mohammad Nasih, S.E., M.T., Ak., CMA, Rector of Universitas Airlangga, for the opportunities given to the author to study at Universitas Airlangga.
4. Prof. apt. Junaidi Khotib, M.Kes., Ph.D., Dean of Faculty of Pharmacy, Universitas Airlangga, for the privilege given to the author to study at the Faculty of Pharmacy, Universitas Airlangga.
5. Prof. Dr. apt. Juni Ekowati, M.Si. s, Head of Department of Pharmaceutical Science, for the facilities provided to the author in completing this thesis.
6. Prof. Dr. Retno Sari, MSc., Apt and Dr. Apt Dewi Isadiartuti, M.Si as the examiners who guided, and advised to the author throughout this thesis completion.
7. Ana Yuda, S.Si., M.Farm., Apt as the author's beloved academic adviser since day one. Thank you for all the patience and kindness in guiding the author towards becoming a better and more responsible student on campus.
8. To all family members, especially Javard, Janie, and Jerene as the author's siblings for their constant motivation and support throughout the author's bachelor's degree journey.
9. Many thanks to SJ Tong and TW Yong as the author's close friends who constantly stood by and supported her through thick and thin.
10. Also, to Hanie Salim and Putu Pradnya who provided valuable opinions, compassion, and understanding throughout the author's entire degree life in Indonesia.
11. My profound thanks to all team members of the research.

12. To all Indonesian classmates and batchmates.
13. Many thanks to Mas Wahda, the assistant supervisor who guided the author through all the laboratory work and the data collection.

May God shower the above-cited personalities with success and honor in their lives. The author acknowledges that this writing is still far from perfection. Despite that, the author hopes this research can be beneficial for the advancement of science, especially in the pharmaceutical field.

Author

SUMMARY

A Study On The Combination Of MCC-PGS And MCC-PVP As Cushioning Agents In MUPS Tablet

Ng Chee Xuan

Multiple Unit Pellet System (MUPS) has emerged as an ideal multiparticulate dosage form, composing pellet as the discrete subunit with a functional coating layer to modify the release of active pharmaceutical ingredients. Nonetheless, the coating layer is prone to stress-induced damage during the compaction of MUPS, causing the drug release behavior to be less favorable.

The incorporation of an excipient functioning as filler named cushioning agent can mitigate the detrimental effect of MUPS compaction. A good cushioning agent should have an average size of less than 20 μm and deform more readily than the pellets at low compaction pressure. Lestari and Heng (2021) have posited that cushioning agents should attain an equilibrium of plastic and brittle deformation to maintain the mechanical integrity of the coating layer during compaction.

In the current study, MCC is chosen as the cushioning excipients owing to its predominantly plastic deforming nature during compaction. MCC has undergone particle size reduction process by wet beads milling as the rough surface of MCC might impart a negative effect on coated pellets. However, it was reported that the plastic deformity nature of MCC has been diminished during the wet process. Consequently, MCC is co-processed with plastic deforming excipients, PVP K30 and Starch 1500, respectively.

The aim of this study is to investigate the combination of co-processed MCC-PVP and MCC-PGS as the cushioning agents to protect the coated pellets and produce stronger MUPS tablets at low compaction pressure with a similar dissolution profile as the uncompacted pellet. To enhance the cushioning effect, the cushioning agent was co-processed by wet beads milling, followed by freeze-drying. Both cushioning agents are characterized by optical microscopy and PXRD. The deformability of cushioning agent was determined by Heckel analysis using an out-of-die approach with a 6mm punch. A plastic material should have a $\text{Py} < 80$. From the optical microscopy, only MCC-PVP possesses an average particle size of less than 20 μm after the co-processing. Meanwhile, the XRD diffractogram clearly indicated that the cellulosic matrix of MCC remained the same after co-processing. The results from the Heckel Plot have indicated that PVP K30 and Starch 1500 have increased the plastic deformability of the respective co-processed cushioning agent.

50% of MCC-PVP and MCC-PGS and 50% of coated pellets were compacted by using a 14 mm punch. In order to yield an intact compact, MCC-PVP and MCC-PGS required a larger compaction force (>2 kN), 8 kN and 5 kN, respectively. The tensile strength and disintegration time of fabricated MUPS were determined, followed by a dissolution test. MCC-PGS has disintegrated less than a minute in average but resulted in a relatively weak tablet (0.18 MPa). MUPS tablet containing MCC-PVP tableted at 8 kN has yielded a weak tablet (0.32 MPa) with a disintegration time of 9 minutes. However, all the fabricated MUPS tablets are deemed weak due to their insufficient mechanical strength (<2 MPa). The dissolution profiles of the MUPS were compared to the

uncompacted coated pellet through T_{50} , similarity factor (f_2), and differential factor (f_1). As compared to the uncompacted pellet, the MUPS tablet produced has a larger T_{50} and showed dissimilarity of dissolution profiles, indicating that both formulations failed to confer cushioning effect on coated pellet.

The co-processed MCC-PVP or MCC-PGS as cushioning agents has been proved to deform plastically but failed to ameliorate the stress-induced damage on coated pellets. Cushioning agent MCC-PVP or MCC-PGS in the ratio of 1:1 have not yielded a strong MUPS tablet at low compaction pressure with dissimilar dissolution profiles as compared to the uncompacted pellets. Prior to modifying the formulation of the cushioning agent, further SEM analysis is needed to investigate the surface morphology of the cushioning agent and the interparticulate bonding in MUPS tablet.

ABSTRACT

A STUDY ON THE COMBINATION OF MCC-PGS AND MCC-PVP AS CUSHIONING AGENTS IN MUPS TABLET

Ng Chee Xuan

This study is to investigate the incorporation of the co-processed cushioning agent in Multiple Unit Pellet System (MUPS) to protect Metformin HCl-coated pellets from compaction-induced damage. To confer protection, a cushioning agent should deform more readily than the coated pellet, resulting in a good balance between plastic and brittle deformability. Apart from its profound plastic deformability, an effective cushioning agent should achieve a smooth surface morphology and be smaller than coated pellet to reduce the degree of pellet damage. Cushioning agents containing microcrystalline cellulose (MCC) with Starch 1500[®] (PGS) or polyvinylpyrrolidone (PVP K 30) in a 1:1 ratio were co-processed by wet beads milling and freeze-drying and compacted with Metformin HCl pellets using 14 mm punch. Both cushioning agents (MCC-PVP and MCC-PGS) exhibited a larger f_1 and a smaller f_2 , indicating a dissimilar dissolution behavior to the uncompacted pellets. The deformation behavior of cushioning agent was analyzed by an Out-die Heckel plot using a 6 mm punch, and the co-processed effect was further characterized by PXRD and optical microscopy. Interestingly, the results obtained from the Heckel plot demonstrated the high plastic deformability of both cushioning agents than untreated MCC and readily deformed at low compression pressure. As plastic deforming excipients ($\phi < 80$), no superior cushioning properties were observed from both co-processed cushioning agents in retaining the mechanical integrity of pellet coating during compaction. Hence, further SEM analysis is supplementary to study the surface morphology of cushioning agent and their interparticulate bonding in MUPS tablet.

Keywords: Cushioning Agent, MUPS tablet, Co-process, MCC-PVP, MCC-PGS

TABLE OF CONTENTS

	Pages
THESIS.....	i
ACKNOWLEDGEMENT	v
TABLE OF CONTENTS	x
LIST OF FIGURES.....	xiii
LIST OF TABLES	xv
LIST OF APPENDICES	xvi
LIST OF ABBREVIATIONS.....	xvii
CHAPTER 1 INTRODUCTION	1
1.1 Research Background.....	1
1.2 Research Problems	4
1.3 Research Objectives	5
1.4 Research Outcomes	5
1.4.1 Theoretical Outcome.....	5
1.4.2 Practical Outcome.....	5
CHAPTER II LITERATURE REVIEW	6
2.1 Multiparticulate Drug Delivery System	6
2.2 Multiple-Unit Pellet System (MUPS)	6
2.2.1 Metformin Hydrochloride (Metformin HCl)	8
2.2.2 Ethyl cellulose	9
2.2.3 Sugar Sphere	10
2.3 MUPS Tablet.....	10
2.4 Challenges in the tableting of MUPS.....	10
2.5 Strategies to overcome problems in compression of MUPS	11
2.6 Cushioning Agent	11
2.6.1 Co-processing Cushioning Agent.....	13

2.6.2	Microcrystalline Cellulose (MCC)	17
2.6.3	Partially Pregelatinized Starch (Starch 1500)	18
2.6.4	Polyvinylpyrrolidone K30 (PVP K30)	20
2.7	Additives.....	21
2.7.1	Magnesium Stearate	21
2.7.2	Sodium Starch Glycolate (SSG).....	22
2.8	Characterization of cushioning agent.....	22
2.8.1	Physical Characterization.....	22
2.8.2	Mechanical Characterization.....	23
2.9	Evaluation of Physical Quality of MUPS Tablet.....	24
2.9.1	Tensile Strength.....	24
2.9.2	Disintegration Time.....	24
2.9.3	Dissolution testing	24
CHAPTER III CONCEPTUAL FRAMEWORK		29
3.1.	Description.....	29
3.2.	Hypothesis	32
3.3.	Flow Diagram of Conceptual Framework.....	33
CHAPTER IV RESEARCH METHODOLOGY		34
4.1.	Materials	34
4.2.	Instrumentation	34
4.3.	Experimental Design.....	34
4.3.1.	Methodology.....	34
4.3.2.	Formula	35
4.3.3.	Variables.....	36
4.3.4.	Operational Framework.....	37
4.4.	Preparation of MUPS tablet Metformin HCl.....	38
4.4.1.	Preparation of Metformin HCl pellet.....	38

4.4.2.	Preparation of cushioning agent	38
4.4.3.	Tableting of coated pellet	39
4.5.	Research Method	39
4.5.1.	Evaluation of Cushioning Agent.....	39
4.5.2.	Evaluation of physicochemical properties of MUPS tablet	42
4.5.4	Dissolution Test	42
CHAPTER V RESULTS AND DISCUSSION.....		45
5.1	Physical Characterization of Cushioning Agent.....	45
5.1.1	Optical Microscopy	45
5.1.2	XRD Diffraction Analysis.....	48
5.2	Mechanical Characterization of Cushioning Agent.....	49
5.2.1	Heckel Analysis	49
5.3	Characterization of MUPS tablet.....	52
5.3.1	Tensile Strength	52
5.3.2	Disintegration Test.....	53
5.3.3	Dissolution Test	54
5.4	Evaluation of Dissolution Profile.....	57
CHAPTER VI CONCLUSION AND SUGGESTION.....		60
6.1.	Conclusion.....	60
6.2.	Suggestion	60
REFERENCES		61
APPENDICES		70

LIST OF FIGURES

	Pages
Figure 2. 1 Structure of MUPS tablet comprising the coated pellet (Bhad et al.,2010).	7
Figure 2. 2 Structure of pellet comprising drug layer and layered with polymeric coating (Al-Hashimi et al., 2018).	7
Figure 2. 3 Schematic representation of a drug-loaded pellet core (Bhad et al., 2010).	7
Figure 2. 4 Schematic representation of polymeric coating on a pellet (Bhad et al., 2010)	8
Figure 2. 5 Chemical structure of Metformin (Apfelbaum, 1978).	8
Figure 2. 6 Chemical structure of ethyl cellulose (Quinten et al., 2021)	9
Figure 2. 7 Stages of compaction of a multiparticulate (Ghebre-Selassie, 1994).	12
Figure 2. 8 Schematic representation of cushioning agent embedded around coated pellets (Bhad et al., 2010)	13
Figure 2. 9 Co-processed excipients with improved functionalities (Parmar et al., 2021).	14
Figure 2. 10 Schematic of reeze-drying events (Carstensen, 2001).	15
Figure 2. 11 SEM picture of an unprocessed MCC (Nemoto et al., 2017).	16
Figure 2. 12 SEM picture of wet-milled MCC (Nemoto et al., 2017).	16
Figure 2. 13 SEM picture of dry-milled MCC (Nemoto et al., 2017).	17
Figure 2. 14 SEM picture of MCC Avicel PH 101 (Gustafsson et al., 2003).	17
Figure 2. 15 SEM photograph of pellets compacted with 1 % MCC (Li et al., 2016).	18
Figure 2. 16 Optical photograph of Starch 1500 (Rojas et al., 2012).	19
Figure 2. 17 SEM photograph of Starch 1500 (Colorcon, 2021)	19
Figure 2. 18 Chemical structure for PVP (Yihong et al., 2017).	20
Figure 2. 19 SEM picture of unprocessed PVP (Siow et al., 2018).	20
Figure 2. 20 SEM picture of freeze-dried PVP (Siow et al., 2018).	21
Figure 2. 21 Chemical structure of magnesium stearate (Hobbs et al., 2017).	21
Figure 2. 22 Chemical structure of SSG (Dilebo and Gabriel, 2019).	22
Figure 5. 1 Optical micrograph of co-processed (a) MCC-PGS and (b) MCC-PVP (c) untreated MCC at a magnification of 100x	46
Figure 5. 2 Particle size distribution of co-processed (a) MCC-PGS and (b) MCC-PVP48	

Figure 5. 3 PXRD diffractogram of untreated MCC, freeze-dried (FD) MCC, and co-processed cushioning agents (MCC-PVP and MCC-PGS)	49
Figure 5. 4 Heckel Plot of reference material (MCC and spray-dried lactose), compared to cushioning agents and their physical mixture	50
Figure 5. 5 Comparison of tensile strength of MUPS tablets	53
Figure 5. 6 Standard calibration curve of Metformin HCl	55
Figure 5. 7 Dissolution profiles of MUPS tablet and uncompacted pellet	56
Figure 5. 8 T50 of MUPS tablet and uncompacted pellet	58

LIST OF TABLES

	Pages
Table IV. 1 Composition Of Cushioning Agent	35
Table IV. 2 Composition Of Each MUPS Tablet	35
Table IV. 3 True Density Value Of Each Exipient	41
Table V. 1 Total Milling Time And The Average Particle Size Of Cushioning Agent	45
Table V. 2 Results Of Out-of-die Heckel Plot	50
Table V. 3 Results Of The Tensile Strength Test Of MUPS Tablets	52
Table V. 4 Results Of The Disintegration Test Of MUPS Tablets	53
Table V. 5 Absorbance of working solutions at different concentrations	54
Table V. 6 Results of dissolution test of MUPS tablet	55
Table V. 7 T50 Of Dissolution Profiles	57
Table V. 8 Results Of The Analysis Of Dissolution Profiles	57

LIST OF APPENDICES

	Pages
1 Measurement of Optical Microscopy	71
2 Results of Particle Size Distribution	77
3 Results of Heckel Analysis	79
4 Results of Standard Calibration Curve Metformin HCl	92
5 Results of Disintegration Test	95
6 Results of Tensile Strength of MUPS	96
7 Results of Dissolution Profile	98
8 Physical Appearance of MUPS Tablet	105

LIST OF ABBREVIATIONS

API	= Active pharmaceutical ingredient
BCS	= Biopharmaceutical classification system
f_1	= Difference factor
f_2	= Similarity factor
K_p	= Out-of-die coefficient
MCC	= Microcrystalline cellulose
Metformin HCl	= Metformin hydrochloride
MgS	= Magnesium stearate
mm	= Millimetre
MUPS	= Multiple-unit pellet system
PMCC-PGS	= Physical mixture of MCC-PGS
PMCC-PVP	= Physical mixture of MCC-PVP
PGS	= Partially pregelatinized starch
PVP	= Polyvinylpyrrolidone
PXRD	= Powder X-ray diffraction
P_y	= Yield pressure
P_{app}	= Apparent density
P_{true}	= True density
SEM	= Scanning electron microscopy
SDL	= Spray-dried lactose
SSG	= Sodium starch glycolate
USP	= United States Pharmacopeia
μm	= Micrometre