



**Preparing diclofenac sodium sustained release tablets using
bentonite by wet granulation**

By

SAIF ALKHALIDI

Supervisor

Prof. AHMAD M.DISI

**This thesis was submitted in partial fulfillment of the requirements for
obtaining a master's degree in pharmaceutical sciences.**

College of Graduate Studies

University of Isra

2019

جامعة الإسراء

نموذج تفويض

أنا سيف الخالدي، أفوض جامعة الإسراء بتزويد نسخة من رسالتي / أطروحتي للمكتبات أو المؤسسات أو الهيئات أو الأشخاص عند طلبها حسب التعليمات النافذة بالجامعة.

التوقيع:

التاريخ:

Isra University

Authorization form:

I, (SAIF ALKHALIDI) Authorize Isra University to supply copies of my thesis /dissertation to libraries or establishment or individuals upon request according to Isra university regulations.

Signature:

Date:

COMMTTEE DECISION

This thesis /Dissertation (Preparing diclofenac sodium sustained release tablets using bentonite by wet granulation) was successfully Defended and Approved.....

Examination Committee Signature

Prof. Ahmad M. Disi (Supervisor)

Dr. Eman Alzmaeli (Internal member)

Dr. Hatem AlKhateeb (External examiner)

Acknowledgment

First of all praise be to Allah, most Gracious, most Merciful, for his unlimited support and favour.

I would like to express my thanks to Dr. Jamal Alyoussef Al –krad and Dr.Ahmad disi my supervisor and head of the department of pharmaceutics, for his wise advices, patience and encouragement throughout all stages of my study.

I am so thankful to college of pharmacy, university of Isra for offering this opportunity to continue my graduate study.

I would like also to express my grateful thanks to my family for their patience, support, help and love.

Finally, I would like to extend my thanks to all others who helped me to finish this work.

Saif A. Alkhalidi

List of Contents

Content	Page
Dedication	I
Acknowledgement	II
List of contents	III
List of figures	VII
List of abbreviations	IX
Abstract	XI

Chapter One	pages
Introduction	2
1.1 Immediate and sustained release dosage form	2
1.2 Sustained Release Formulation	3
1.3 Diclofenac sodium	5
1.3.1 Diclofenac sodium structure, physicochemical properties pharmacological effects and side effects	5
1.3.2 Available Diclofenac formulations and forms (Altman et al., 2015)	6
1.4 Bentonite and previous studies	7
1.5 Objectives	9

Chapter two	Pages
2. Materials and instruments	11
2.1 Materials	11
2.2 Methods and instruments	11
2.2.1 Wet granulation and tableting	11
2.2.2 Flowability measurement	13
2.2.3 Measuring fragility	13
2.2.4 Hardness measuring	13
2.2.5 Dissolution test performance and sampling	14
2.2.6 High pressure liquid chromatogram (HPLC) assay	14
2.2.7 Enteric coating using Eudragit	14
2.2.8 Enteric coated tablets evaluation	15
2.2.9 Statistical evaluation	16

Chapter Three	
3. Results	18
3.1 HPLC method and calibration curve	18
3.2 Flowability of granule	19

3.3 Tablet quality control	20
3.4 Dissolution behavior of uncoated tablets	21
3.5 Dissolution behavior of enteric coated tablets	26

Chapter Four	
Discussion	31

Chapter Five	
5.Conclusion	36

Chapter six	
References	38

List of tables

Table	Title	Page
1.	Composition of formulated tablets	12
2.	EUDRAGIT® L 30 D-55 on particles (1 kg), top spray	15
3.	The flowability evaluation using CAR's index and Hausner ratio	20
4.	The hardness and friability of prepared tablets	20
5.	Similarity factor between the different tablets and the reference.	29
6.	The linearity between the time and percentage cumulative released amounts	31

List of figure

Figure	Title	Page
1.	Plasma concentration of drugs for traditional tablet installations, formulation of steady release and zero-release formula control.	3
2.	Structural formula of diclofenac sodium (Budavari, 2001:542).	5
3.	Chromatograms of DS using HPLC	18
4.	Calibration curve of DS using HPLC-method	19
5.	Dissolution profile of tablets containing DS (weighing 250 mg) prepared using PVP as binder	21
6.	Dissolution profile of tablets containing DS (weighing 250 mg) prepared using PVP as binder.	22
7.	Dissolution profile of tablets containing DS (weighing 250 mg) prepared using PEG400 as binder.	23
8.	Dissolution profile of tablets containing DS (weighing 250 mg) prepared using water without any binder.	24
9.	Dissolution profile of tablets containing DS prepared using water (weighing 250 mg) in HCL 0.1N for two hours then in phosphate buffer pH of 7.5	25
10.	Dissolution profile of a reference tablets containing DS (weighing 250 mg) in phosphate buffer pH of 7.5.	26
11.	Dissolution profile of a reference tablets containing DS (weighing 250 mg) in phosphate buffer pH of 7.5.	27

12.	Dissolution profile of different uncoated tablets compared to the reference.	28
13.	Dissolution profile of different uncoated tablets compared to the reference.	32
14.	Gel structure of bentonite tablets	33
15.	Dissolution profile of enteric coated tablets compared the reference.	34

Abbreviation

AUC	Area under the curve
B	Bentonite
C_p	Plasma concentration
DS	Diclofenac sodium
DSC	Differential scanning calorimetry
hr	Hour
ICH	International Comity for harmonization
MPS	Multi particulate system
MTC	Minimum toxic concentration
MEC	Minimum effective concentration
MDT	Mean dissolution time
NSAID	Non-steroidal anti-inflammatory drug
PVP	Polyvinylpyrrolidone
PEG	Poly ethylene glycol

Preparing diclofenac sodium sustained release tablets using bentonite by wet granulation

By

SAIF ALKHALIDI

Supervisor

Prof. AHMAD M.DISI

Abstract

This study is designed to employ bentonite to develop and optimize multiparticulate drug delivery system by wet granulation method for preparing controlled release diclofenac sodium tablets. In this study the pharmacopoeial HPLC method were verified for analyzing diclofenac sodium according to International conference on harmonisation (ICH) guidelines (Q2 R1). Also, the use of different binders in preparing Multi particulate system (MPS) with sodium diclofenac was investigated to identify their impact on tablets properties including drug release. The, produced tablets were evaluated regarding their mechanical strength by measuring the hardness and the friability. Furthermore, the tablets were protected from gastric juice using enteric coating then the coating was assessed. Besides, the similarities of our enteric coated formulated tablets with a reference were calculated.

The formulated tablets complied with pharmacopeial requirements. Furthermore, we demonstrated sustained release for 16 hrs at least with similarity factor higher than 50% dissolve of the drug. The developed tablets using bentonite by wet granulation are good candidate for further in vivo evaluation.