



DESIGN, DEVELOPMENT AND EVALUATION OF
GASTRORETENTIVE DRUG DELIVERY SYSTEM
OF METFORMIN HCL

BY

FARIA GIAS SENJOTI

A thesis submitted in fulfilment of the requirement for
the degree of Master in Pharmaceutical Science
(Pharmaceutical Technology)

Kulliyyah of Pharmacy
International Islamic University Malaysia

JULY 2014

ABSTRACT

Metformin HCl, a drug from biguanide class, is the most commonly used first-line antihyperglycemic agent in the treatment of NIDDM. The major problems associated with the drug are high dose (1.5-2.0 g/day), frequent dosing due to its shorter biological half-life (1.5-4.9 hr), and low bioavailability (60%). Low bioavailability of metformin results from incomplete absorption of the drug as metformin is majorly absorbed from stomach and lower part of GIT. The study was done for the purpose of developing gastroretentive tablets of metformin HCl to prolong gastric residence time and increase drug bioavailability based on polymer swelling and gas formation. Combination of HPMC and polyethylene oxide was used as both matrix forming agent and swelling agent, while sodium bicarbonate as gas forming agent. Drug-excipient incompatibility was confirmed by DSC and FTIR study. 12 mm circular bi-convex floating tablets were prepared by wet granulation method using a 10-station Rotary tablet press machine. Fabricated tablets were optimized by response surface methodology (RSM) utilizing Box Behnken experimental design. Seventeen (17) trial formulations were investigated taking various compositions of polymer, NaHCO₃ and SSG each at three levels. Data analysis and modeling were performed by Design expert® software (version 8.0.7.1, stat-Ease Inc., Minneapolis, MN). The optimized tablets were evaluated for weight variation, hardness, thickness, friability, moisture content, assay, *in-vitro* floating lag time, % swelling and surface morphology study. Furthermore, optimized tablets were stored at accelerated stability condition (40 °C and 75% RH) for 3 months. All preformulation parameters were found to be within the acceptable range. Melting peaks of metformin was visible in DSC thermogram of drug-excipients mixture, indicating that metformin was compatible with the rest of the excipients of formulation. FTIR study also confirmed the same finding. Floating lag time and duration of floating were found to be dependent on amount of gas effervescent agent (NaHCO₃), swelling of polymers (HPMC and PEO) and swelling enhancer (SSG). It was found that formulation with of polymer concentration 250 mg, NaHCO₃ 60 mg, and SSG 50 mg fulfilled requisites of an optimum formulation. The optimized formulation was found to provide average floating lag time less than 4 minutes with a floating duration of more than 24 hours. Swelling rate of the combination of polymers was found to be rapid and linear for initial 2 hr, however it decreased thereafter and maintained the linearity until 8 hours. Combination of HPMC and PEO allowed efficient control of drug release for 12 hours. SEM figure showed the non-porous nature of tablet outer surface and little bit porous structure of inner surface before dissolution study. However, after dissolution of 2 hours and 8 hours, both surfaces turned into porous structure which allows the drug to diffuse to the surrounding medium. This also proved that the drug release occurs by diffusion. Based on accelerated stability study; optimized formulation was found to be stable for three months without any major changes in assay, dissolution profile, floating lag time and other physical properties.

ملخص البحث

الميتفورمين حمض الهيدروكلوريك، وهو دواء من فئة biguanide، هو الأكثر شيوعاً الخط الأول وكيل خافض سكر الدم في علاج NIDDM. المشاكل الرئيسية المرتبطة بالمخدرات هي جرعة عالية (1.5-2.0 غ / يوم)، جرعات متكررة بسبب أقصر البيولوجية نصف حياتها (1.5-4.9 ساعة)، والتوافر البيولوجي منخفضة (60%). يمتص التوافر البيولوجي منخفض من النتائج الميتفورمين من امتصاص غير مكتملة من المخدرات كما الميتفورمين مجوري من المعدة والجزء السفلي من الجهاز الهضمي. تم إجراء دراسة لغرض تطوير أقراص الميتفورمين gastroretentive من حمض الهيدروكلوريك لإطالة فترة بقائه في المعدة وزيادة التوافر البيولوجي المخدرات استناداً إلى تورم البوليمر وتشكيل الغاز. تم استخدام مزيج من أكسيد HPMC والبولي إثيلين على حد سواء مصفوفة تشكيل كيل وتورم وكيل، في حين بيكربونات الصوديوم كعامل تشكيل الغاز. وأكد المخدرات سواغ عدم التوافق التي كتبها DSC ودراسة FTIR. وبطريقة التحبيب الرطب إعداد أقراص دائرية 12 ملم العائمة ثنائية محدة باستخدام 10 محطة الروتاري قرص الصحافة الآلة. تم الأمثل أقراص ملفقة من قبل منهجية استجابة السطح (RSM) باستخدام صندوق بينكين التصميم التجريبي. وقد تم التحقيق سبعة عشر (17) تركيبات محاكمة اتخاذ تركيبة مختلفة من البوليمر، NaHCO_3 و SSG كل على ثلاثة مستويات. تم إجراء تحليل البيانات والنمذجة خبير تصميم البرمجيات R^2 (الإصدار 8.0.7.1، القانون الأساسي لسهولة شركة، مينيابوليس، مينيسوتا). تم تقييم أقراص الأمثل لاختلاف الوزن، والصلابة، وسمك، تفتيت، ومحتوى الرطوبة، الفحص، في المختبر العائمة الوقت الضائع،% التورم ودراسة مورفولوجية السطح. علاوة على ذلك، تم تخزين أقراص الأمثل في حالة الاستقرار المعجل (40 درجة مئوية و 75% RH) لمدة 3 أشهر. تم العثور على جميع العلامات preformulation لتكون ضمن النطاق المقبول. ذوبان قمع الميتفورمين كان مرئياً في DSC-حراري من السواغات المخدرات خليط، مشيراً إلى أن الميتفورمين كانت متوافقة مع ما تبقى من السواغات صياغة. كما أكدت الدراسة FTIR نفس النتيجة. تم العثور العائمة الوقت الضائع ومدة العائمة أن تعتمد على كمية الغاز كيل فوارة (NaHCO_3)، وتورم للبوليمرات (PEO و HPMC) وتورم محسن (SSG). تبين أن صياغة مع تركيز البوليمر 250 ملغ، 60 ملغ NaHCO_3 ، و 50 SSG ملغ الوفاء requisites لصياغة الأمثل. تم العثور على صياغة الأمثل لتوفير الوقت الضائع متوسط العائمة أقل من 4 دقائق مع مدة عائمة لأكثر من 24 ساعة. وجد تورم معدل مزيج من البوليمرات ليكون سريعاً وخطية للعسل 2 ساعة، إلا أنه انخفض بعد ذلك وحافظت على الخطي حتى 8 ساعات. . يسمح الجمع بين HPMC و PEO مراقبة فعالة من الإفراج عن المخدرات لمدة 12 ساعة. أظهر الرقم SEM طبيعة غير قابلة للاختراق من قرص السطح الخارجي وقليلاً مسامية بنية السطح الداخلي قبل دراسة حل. ومع ذلك، وبعد انحلال 2 ساعة و 8 ساعات، وتحولت كل السطوح في بنية مسامية الذي يسمح لنشر المخدرات إلى الوسط المحيط. هذا يثبت أيضاً أن الإفراج عن المخدرات يحدث من قبل نشرها. استناداً إلى دراسة الاستقرار تسارع؛ وجد صياغة الأمثل لتكون مستقرة لمدة ثلاثة أشهر دون أي تغييرات كبيرة في الفحص، لحة حل، وتطفو الوقت الضائع والخصائص الفيزيائية الأخرى..

APPROVAL PAGE

I certify that I have supervised and read this study and that in my opinion, it conforms to acceptable standards of scholarly presentation and is fully adequate, in scope and quality, as a thesis for the degree of Master of Pharmaceutical Science (Pharmaceutical Technology).

.....
Uttam Kumar Mandal
Supervisor

I certify that I have read this study and that in my opinion it conforms to acceptable standards of scholarly presentation and is fully adequate, in scope and quality, as a thesis for the degree of Master of Pharmaceutical Science (Pharmaceutical Technology).

.....
Bappaditya Chatterjee
Internal Examiner

.....
Saringat bin Bai @ Baje
External Examiner

This thesis was submitted to the Department of Pharmaceutical Technology and is accepted as a fulfilment of the requirement for the degree of Master of Pharmaceutical Science (Pharmaceutical Technology).

.....
Juliana Md. Jaffri
Head, Department of
Pharmaceutical Technology

This thesis was submitted to the Kulliyah of Pharmacy and is accepted as a fulfilment of the requirement for the degree of Master of Pharmaceutical Science (Pharmaceutical Technology).

.....
Siti Hadijah Shamsudin
Dean, Kulliyah of Pharmacy

DECLARATION

I hereby declare that this thesis is the result of my own investigation, except where otherwise stated. I also declare that it has not been previously or concurrently submitted as a whole for any other degrees at IIUM or other institutions.

Faria Gias Senjoti

Signature.....

Date

INTERNATIONAL ISLAMIC UNIVERSITY MALAYSIA

**DECLARATION OF COPYRIGHT AND AFFIRMATION
OF FAIR USE OF UNPUBLISHED RESEARCH**

Copyright ©2014 by Faria Gias Senjoti. All rights reserved.

**DESIGN, DEVELOPMENT AND EVALUATION OF GASTRORETENTIVE
DRUG DELIVERY SYSTEM OF METFORMIN HCL**

No part of this unpublished research may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, recording or otherwise without prior written permission of the copyright holder except as provided below.

1. Any material contained in or derived from this unpublished research may be used by others in their writing with due acknowledgement.
2. IIUM or its library will have the right to make and transmit copies (print or electronic) for institutional and academic purposes.
3. The IIUM library will have the right to make, store in a retrieval system and supply copies of this unpublished research if requested by other universities and research libraries.

Affirmed by Faria Gias Senjoti

.....
Signature

.....
Date

ACKNOWLEDGEMENTS

All praise is due to Allah S.W.T because of His bounty I can complete this research towards fulfilling the requirements for my master degree, Alhamdulillah. May Allah provide benefits from this research to those who seek knowledge and make this research as a reason for others to increase their Iman towards HIM.

I would like to express my gratitude to my parents, for their moral supports that gave me the confidence, will and strength to endure pressure and tension in pursuing my ambition. Also, I would like to express my most sincere gratitude to supervisor, Assistant professor Dr. Uttam Kumar Mandal for helping me and giving me guidance throughout the research and giving me endless advises in completing this thesis; Assistant Professor Dr. Juliana Md. Jaffri for her help and guidance throughout this work at the Kulliyah of Pharmacy, International Islamic University Malaysia, Kuantan.

My thanks to Dr. Muhammad Taher for his assistance. Next, I want to express my gratitude to all lab assistants who were involved in this research especially Sis. Haryanti, Br. Dza dil, our science officers of Pharmaceutical Technology Department, Sis. Zaililah, Sis. Haslina and Sis Syuhaiha for their assistances during the time of thesis work.

Thanks to Sis. Thazin, Sis. Afnan, Sis. Azmir, Sis Hasna, Br. Mahmood, Br. Sharif, Sis. Tasnuva and Sis. Mehnaz for helping me a lot during the research. May Allah give His blessings in their lives in this world.

TABLE OF CONTENTS

Abstract.....	ii
Abstract in Arabic.....	iii
Approval page.....	iv
Declaration page.....	v
Copyright page.....	vi
Acknowledgements.....	vii
List of Tables.....	xii
List of Figures.....	xiv
List of Equations.....	xvii
List of Abbreviations.....	xviii
CHAPTER 1: INTRODUCTION.....	1
1.1 Research Background.....	2
1.2 Metformin HCl: Drug of choice.....	6
1.3 Statement of the problem and research objectives.....	7
CHAPTER 2: LITERATURE REVIEW.....	10
2.1 Gastroretentive drug delivery system (GRDDS).....	10
2.1.1 Anatomy and Basic Physiology of the Stomach.....	10
2.1.2 Factors affecting Gastric Retention.....	14
2.1.2.1 Formulation factors.....	14
2.1.2.2 Idiosyncratic factors.....	16
2.1.3 Multifarious uses of GRDDS.....	17
2.1.4 Limitation of gastroretentive drug delivery system.....	19
2.1.5 Approaches of GRDDS.....	20
2.1.5.1 Floating drug delivery systems (FDDS).....	21
2.1.5.1.1 Gas-generating system.....	21
2.1.5.1.2 Raft forming systems.....	22
2.1.5.1.3 Low density systems.....	23
2.1.5.1.4 Hydrodynamically balanced systems : HBS.....	24
2.1.5.1.5 Swelling and expanding system.....	25
2.1.5.2 Mucoadhesive or bioadhesive systems.....	27
2.1.5.3 High density systems.....	28
2.1.5.4 Modified systems.....	29
2.1.5.5 Super porous hydrogel systems.....	29
2.1.5.6 Magnetic systems.....	30
2.1.6 Literature review on GRDDS.....	30
2.1.6.1 HPMC.....	31
2.1.6.1.1 Physicochemical properties.....	32
2.1.6.1.2 GRDDS with HPMC.....	32
2.1.6.2 Polyethylene oxide.....	34
2.1.6.2.1 Physicochemical properties:.....	35
2.1.6.2.2 GRDDS with polyox.....	35
2.1.6.3 GRDDS with other polymers.....	36
2.2 Diabetes: An overview.....	38

2.2.1 Recent statistics on diabetes	39
2.2.2 Development of diabetes	39
2.2.3 Type I diabetes	40
2.2.4 Type II diabetes	41
2.2.5 Gestational diabetes	41
2.2.6 Treatment Option of diabetes	42
2.2.6.1 Diet	42
2.2.6.2 Exercise	43
2.2.6.3 Insulin	43
2.2.6.4 Oral hypoglycemic therapy	43
2.3 Drug Profile: Metformin HCl	44
2.3.1 Molecular formula	44
2.3.2 Molecular weight.....	44
2.3.3 Physicochemical properties	44
2.3.4 Pharmacokinetics.....	44
2.3.5 Mechanism of action	45
2.3.6 Indication.....	46
2.3.7 Contraindications:.....	46
2.3.8 Adverse effects	46
2.3.9 Interactions	46
CHAPTER 3: METHODOLOGY.....	47
3.1 Materials.....	47
3.2 Methods.....	48
3.2.1 Preformulation studies.....	48
3.2.1.1 Physicochemical characterization of drug and excipients.....	48
3.2.1.2 Development of analytical method estimation of MTH.....	48
3.2.1.2.1 Preparation of dilutions for calibration.....	49
3.2.1.2.2 Determination of λ_{\max}	49
3.2.1.2.3 Preparation & validation of Calibration curve	49
3.2.1.3 Drug-excipient compatibility by DSC and FTIR study.....	50
3.2.2 Formulation	50
3.2.2.1 Preparation of the gastroretentive tablets	50
3.2.2.2 Determination of micromeritic properties of granules	51
3.2.2.2.1 Angle of repose.....	51
3.2.2.2.2 Bulk and tapped density	52
3.2.2.2.3 Compressibility index (Carr's index).....	52
3.2.2.2.4 Hausner ratio	52
3.2.2.3 Drug release study	52
3.2.2.4 In vitro buoyancy determination	53
3.2.2.5 Determination of the effect of polymers, swelling enhance and effervescent component on drug release and floating lag time.....	54
3.2.2.5.1 Effect of polyox and HPMC concentration on drug release and floating lag time.....	54
3.2.2.5.2 Effect of SSG on drug release and floating lag time	55
3.2.2.5.3 Effect of NaHCO ₃ on drug release and floating lag time.....	55
3.2.3 Optimization of the formulation using Response Surface Methodology (RSM).....	56

3.2.3.1 Experimental trials according to Box-Behnken design	57
3.2.3.2 Data analysis and validation of RSM model	58
3.2.3.3 Mathematical modeling of drug release kinetics	59
3.2.4 Characterization of the optimized gastroretentive tablets	60
3.2.4.1 Tablet hardness and thickness	60
3.2.4.2 Friability	60
3.2.4.3 Drug Content	61
3.2.4.4 Moisture content	61
3.2.4.5 Comparison with commercial product	61
3.3 Surface morphology study of the Gastro retentive tablet by SEM	62
3.4 Determination of percentage of swelling index	62
3.5 Stability studies	63
CHAPTER 4: RESULTS & DISCUSSION	64
4.1 Preformulation	64
4.1.1 Physicochemical characterization	64
4.1.2 Development of analytical method.....	65
4.1.3 Analytical method validation	65
4.1.4 Drug-excipients compatibility study by DSC and FTIR	66
4.2 Formulation.....	75
4.2.1 Determination of the micromeritic properties of granules	75
4.2.2 Determination of the effect of polymers, swelling enhancer and effervescent component on drug release and floating lag time.....	77
4.2.2.1 Effect of polyox and HPMC concentration on drug release and floating lag time	77
4.2.2.2 Effect of SSG concentration on drug release and floating lag time.....	79
4.2.2.3 Effect of NaHCO ₃ concentration on drug release and floating lag time	80
4.3 optimization of grdds of mth by response surface methodology (RSM)...	85
4.3.1 Responses/results of dependent variables for all experimental trials.	82
4.3.2 Mathematical modeling	85
4.3.2.1 Floating lag time (Y ₁).....	86
4.3.2.2 Cumulative % of drug release in 2 h (Y ₂)	89
4.3.2.3 Cumulative % of drug release in 12 h (Y ₃)	92
4.3.3 Internal validation of the model	95
4.3.4 Selection of the optimized formulation	95
4.3.5 Mathematical modeling of drug release profile.....	98
4.4 Characterization of the optimized formulation	99
4.5 Comparison of <i>in-vitro</i> drug release profile of the optimized with commercial product	101
4.6 Surface morphology study by SEM.....	102
4.7 Determination of percentage of swelling index	104
4.8 Stability studies	105
CHAPTER V: CONCLUSION	109
5.1 Future studies.....	111
REFERENCES	112

PUBLICATIONS AND PRESENTATIONS.....126

LIST OF TABLES

<u>Table No.</u>		<u>Page No.</u>
2.1	Description of four phases of MMC	12
2.2	Marketed GRDDS	19
2.3	Mechanisms of dosage form to adhere to the mucosal surface	28
3.1	Drug and excipients	49
3.2	Apparatus and equipments	50
3.3	Formulation of gastroretentive tablet of MTH	53
3.4	Composition of trial batches (different ratios of Polyox and HPMC)	57
3.5	Composition of trial batches (different concentrations of SSG)	58
3.6	Composition of trial batches (different concentrations of NaHCO ₃)	58
3.7	Variables in Box-Behnken design for preparation of GRDDS of MTH	59
3.8	Three level three factor BBD	60
4.1	Physicochemical properties of drug and excipients	67
4.2	Interday and intraday precision of Spectrophotometric method for metformin HCl	69
4.3	Micromeritic properties of the granules	79
4.4	Flow Properties and Corresponding Angles of Repose	79
4.5	Scale of Flowability	79
4.6	Effect of polyox and HPMC concentration on floating lag time	82
4.7	Effect of SSG concentration on floating lag time	83

4.8	Effect of different NaHCO ₃ concentration on floating lag time	85
4.9	Independent variables and responses experimental trials as per Box behnken design	87
4.10	Analysis of Variance (ANOVA) of all three response variables as per Box-Behnken design	89
4.11	Summary of mathematical modeling of release profile of an optimized formulation	99
4.12	Physical characterization of optimized gastroretentive tablet of metformin HCl	99
4.13	Results of accelerated stability study	109
4.14	Observed values for similarity factor (f ₂)	110

LIST OF FIGURES

<u>Figure No.</u>		<u>Page No.</u>
1.1	Differences among various drug release profile	3
1.2	Drug absorption in: (A) conventional dosage form and (B) the gastroretentive drug delivery system	5
2.1	Diagram of human stomach	11
2.2	Motility patterns of the GIT in fasted state	14
2.3	Schematic representation of gas generating system	22
2.4	Schematic illustration of the barrier formed by a raft-forming system	23
2.5	Microballoons	24
2.6	Hydrodynamically balanced system (HBS)	25
2.7	Swellable systems	26
2.8	Unfoldable gastroretentive systems	27
2.9	Bioadhesive drug delivery through gastric mucosa	28
2.10	Schematic localization of an intragastric floating system and a high density system in the stomach	29
2.11	Superporous hydrogel based drug delivery system	30
2.12	Chemical structure of HPMC	32
2.13	Chemical structure of Polyox	35
2.14	Numbers of adult with diabetes in developed and developing countries	40
2.15	Chemical structure of Metformin HCL	45
4.1	Calibration curve of Metformin HCl using UV spectrophotometry	68
4.2	DSC thermogram of Metformin HCl	70

4.3	DSC thermogram of (a) HPMC (b) MTH-HPMC (c) Polyox (d) MTH-Polyox	71
4.4	DSC thermogram of (a) SSG (b) MTH-SSG	72
4.5	DSC thermogram of (a) PVP (b) MTH-PVP	73
4.6	DSC thermogram of (a) mg stearate (b) MTH-mg stearate	74
4.7	DSC thermogram of (a) NaHCO ₃ (b) MTH-NaHCO ₃ (c) MTH-all excipients	75
4.8	IR spectra of (a)MTH (b)NaHCO ₃ (c) HPMC (d) PVP	76
4.9	IR spectra of (a)SSG (b) talc (c) polyox	77
4.10	IR spectrum of MTH and all excipients	78
4.11	Effect of polymer concentration on drug release profile	81
4.12	Effect of SSG concentration of drug release	83
4.13	Effect of Sodium bi carbonate on drug release	84
4.14	Effect of polymer concentration on drug release profile	86
4.15	3-D-response surface plot showing effect of independent variables A, B, and C on floating lag time (Y_1)	87
4.16	Contour plot showing relationship between various level of factor A, B, and C on floating lag time (Y_1).	88
4.17	3-D-response surface plot showing effect of independent variables A, B, and C on % drug released in 2 h (Y_2)	90
4.18	Contour plot showing relationship between various levels of factor A, B, and C on % drug released in 2 h (Y_2).	91
4.19	3-D-response surface plot showing effect of independent variables A, B, and C on % drug released in 12 h (Y_3)	93
4.20	Contour plot showing relationship between various levels of factor A, B, and C on % drug released in 12 h (Y_3)	94
4.21	Linear correlation plots between predicted and actual values of Y_1 , Y_2 and Y_3	102
4.22	Floating behavior of GR tablet	103

4.23	Comparative dissolution profile of the optimized formulation and the marketed product	104
4.24	Surface and cross sectional morphology by using SEM	106
4.25	Swelling index study of GR tablet of MTH in 0.1N HCl	107
4.26	Results of accelerated stability study	110
4.27	DSC thermogram of the formulation after stability study	111
4.28	IR spectra of the formulation after stability study	110

LIST OF EQUATIONS

<u>Equation No.</u>	<u>Page No.</u>
3.1	54
3.2	54
3.3	55
3.4	55
3.5	56
3.6	61
3.7	62
3.8	62
3.9	62
3.10	62
3.11	64
3.12	64
3.13	66
4.1	88
4.2	88
4.3	88

LIST OF ABBREVIATIONS

ANOVA	Analysis of variance
BBD	Box behnken design
CDER	Centre for drug evaluation & research
CMC	Carboxymethylcellulose
DSC	Differential scanning calorimetry
DCP	Dicalcium phosphate
FDDS	Floating drug delivery system
FDA	Food and drug administration
FTIR	Fourier transform infrared
GRDDS	Gastroretentive drug delivery system
GRDF	Gastroretentive dosage form
GDM	Gestational diabetes
GIT	Gastrointestinal tract
HPMC	Hydroxypropylmethylcellulose
HEC	Hydroxyethylcellulose
HPC	Hydroxypropylcellulose
HBS	Hydrodynamically balanced system
HQC	High quality control concentration
IDDM	Insulin dependent diabetes mellitus
IPA	Isopropyl alcohol
LBD	Low bulk density
LQC	Low quality control concentration
MLRA	Multiple linear regression analysis

MTH	Metformin Hydrochloride
MMC	Migrating motor complex
MQC	Medium quality control concentration
NIDDM	Non insulin dependent diabetes mellitus
NCE	New chemical entity
NDDS	Novel drug delivery system
NACMC	Sodiumcarboxymethylcellulose
PEO/POLYOX	Polyethyleneoxide
PVP	Polyvinyl pyrrolidone
RSM	Response surface methodology
RPM	Rotations per minute
SSG	Sodium starch glycolate
SEM	Scanning electron microscope
TBD	Tapped bulk density

CHAPTER ONE

INTRODUCTION

The past several years have witnessed great advances in the development of the novel drug delivery system (NDDS) (Ajazuddin & Saraf, 2010). NDDS offers tremendous commercial profit to the Pharmaceutical industries as an existing drug molecule can get a new life in that improvised form. Along with its market value, the same old drug enjoys competitiveness and its patent life is extended. The development of a new chemical entity (NCE) requires an expenditure of approximately \$800 million and time period of around 10-12 years, whereas for a novel drug delivery system (NDDS) the requirement is approximately \$20-50 million and 3-4 years respectively (Zhang et al., 2013). So in the near future, the approval of NDDS is expected to continue at a considerable rate. When an existing medicine is incorporated into a new drug delivery system, safety, efficacy and also patient compliance can be notably improved. In the NDDS era, multiple platform technologies are being developed for controlled release, delivery of large molecules, liposomes, technology for insoluble drugs. The same old drugs are being tried to deliver through different routes to improve therapeutic efficacy and patient compliance. A number of techniques such as osmotic pump system, gastric retention system, and reduced irritation system have been exploited commercially to achieve controlled release of drugs when administered orally (Verma & Garg, 2001). Thus NDDS has opened a new avenue to formulation scientists, and this trend is expected to continue in the near future as well.

1.1 RESEARCH BACKGROUND

Different conventional pharmaceutical dosage forms are used as drug carriers for many decades to accomplish the treatment of chronic or an acute illness. These dosage forms include tablets, pills, capsules, creams, suppositories, ointments, aerosols, injectables and liquids (Yie, 1992; Chen et al., 2013). Drug may be administered by variety of routes but oral administration is mostly preferred wherever possible because it offers ease of administration, flexibility in formulation and also patient compliance (Garg & Sharma, 2003). From immediate release to site specific drug delivery, oral route of administration has by far received the most attention with respect to research on design and testing of products in spite of physiological and drug constraints (Chien, 1992; Leon et al., 1987). Once administered in the GIT, drug release from the dosage forms follows various release kinetics depending on the design matrix.

Tablets and capsules represent the preferred class of dosage forms that are administered orally. However, between these two, the tablets have number of advantages like flexibility in formulation, ease of administration, patient compliance, low cost and speed of manufacturing (Aulton, 2007; Leon et al., 1991; Rawlins, 2010).

The aim of any drug delivery system is to draw out desired pharmacological action by providing a therapeutic amount of drug to the appropriate site of the body, to attain therapeutic action quickly and then continue the same for a certain period according to the need of the therapy. Another important strategy of ideal drug delivery system is to design a dosage form with single dose or less frequent dosing interval. Instead of conventional immediate release dosage forms, a suitably designed controlled and sustained release dosage form can be a major advance in this direction (Borase, 2012). Figure 1.1 shows the differences of drug release profile from

immediate release, sustained release and controlled release medication. In the controlled release drug delivery system, drug is released at a predetermined, predictable and controlled rate. Different benefits can be achieved through this delivery system like (Chien, 1992);

1. Optimum therapeutic drug concentration in blood for the prolonged period.
2. Prolonged duration of activity for short half-life drugs.
3. Minimum side effects.
4. Reduced dosing frequency

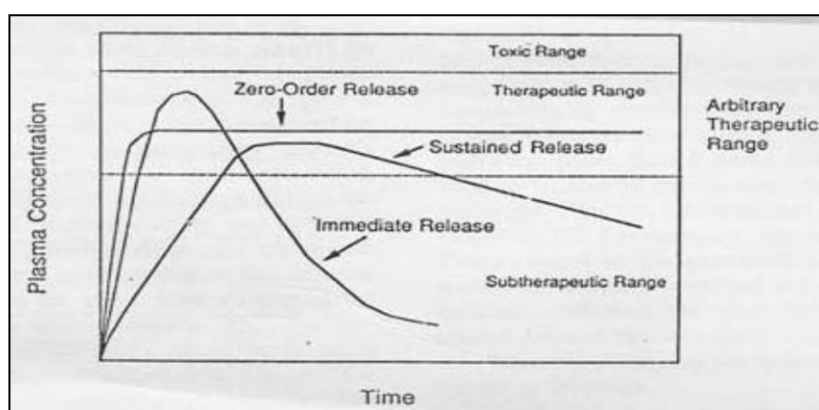


Figure 1.1. Differences among various drug release profile (Narang, 2011)

To achieve improved and expected bioavailability is the primary aim in designing an oral controlled drug delivery system (Kumar & Philip, 2007). However, the real challenge lies in sustaining the drug release as well as extending the residence of dosage form in the stomach or small intestine until the drug is entirely released in desired period of time (Patil et al., 2006). In order to address those issues, a number of different oral controlled drug delivery systems have been developed based on different modes of operation, for example, dissolution controlled system, diffusion

controlled system, ion-exchange resins, osmotically controlled system, erodible matrix system, pH-independent formulation and swelling controlled system (Sen et al., 2005). But most of the systems encounter a wide range of highly inconsistent conditions, like pH, agitation intensity, and composition of gastrointestinal fluid as they pass down the GIT. They also experience several physiological difficulties like extremely variable nature of gastric emptying process and incapability to localize and retain the drug delivery system within desired regions of GIT (Shah & Pandya, 2010). The residence time in stomach is one of the significant determinants of GI transit (Timmermans et al., 1989). It has been reported by various researchers that GI transit time adversely affects the performance of an oral controlled drug delivery system (Singh & Kim, 2000; Streubel et al., 2003). It has been established that GI transit time depends on the physical properties of the object ingested and the physiological condition of gut, both of which vary extensively between individuals. This variability may lead to unpredictable bioavailability and time to attain peak plasma levels.

So in order to achieve an expected and extended drug release profile in GIT, control of the gastric residence time (GRT) is one of the most realistic approaches. Similarly, for local action in the upper part of the small intestine, for example treatment of peptic ulcer disease, longer residence time in the stomach could be beneficial. In addition to this, for drugs that are absorbed readily upon release in GIT, enhanced bioavailability could be possible (Gutierrez-Rocca et al., 2003).

Recently huge interest has grown among formulation scientists to design NDDS that are retained in the stomach for a extended and predictable period of time and release the drug in a controlled manner (Dixit et al., 2009; Streubel et al., 2003). Gastro retentive drug delivery system (GRDDS) thus is one of the novel approaches embraced by the formulation scientists to overcome important challenges associated

with oral drug delivery (Aterman, 2007). Like all other sustained release preparations, GRDDS also continuously releases the drug for a prolonged period, but limited to stomach and lower part of intestine and thus ensures optimal bioavailability (Tayade, 2003). So, they not only avoid frequent dosing intervals, but also enhance patient compliance beyond the level of existing controlled release dosage forms (Kumar et al., 2012). Figure 1.2 shows the differences in drug absorption between conventional dosage forms and GRDDS.

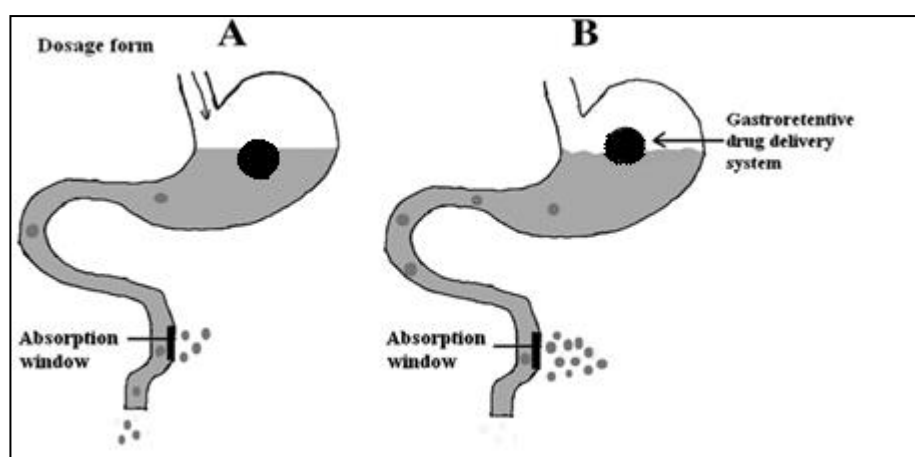


Figure 1.2. Drug absorption in: (A) conventional dosage form and (B) the gastroretentive drug delivery system (Kumar & Philip, 2007)

The present research work was an attempt to design a formulation of gastro retentive drug delivery system of Metformin HCl (MTH) with the aim of improving its oral bioavailability. This anti diabetic drug is the most widely used one and it works by improving peripheral glucose uptake as well as by reducing hepatic glucose in patients with non insulin dependent diabetes mellitus (NIDDM) or type II diabetes (Grisouard et al., 2010).