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

BY

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

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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, $NaHCO_3$ 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 ($NaHCO_3$), swelling of polymers (HPMC and PEO) and swelling enhancer (SSG). It was found that formulation with of polymer concentration 250 mg, $NaHCO_3$ 60 mg, and SSG 50 mg fulfilled requistes 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.

ملخّص البحث

الميتفورمين حمض الهيدروكلوريك، وهو دواء من فئة biguanide، هو الأكثر شيوعا 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 مجورلي 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 استنادا إلى تورم البوليمر وتشكيل الغاز. تم استخدام مزيج من أكسيد HPMC والبولي اثيلين 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 محدبة 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، $NaHCO_3$ وSSG كل على ثلاثة مستويات. تم إجراء تحليل البيانات والنمذجة خبير تصميم البرمجيات ® (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 المعلمات preformulation لتكون ضمن النطاق المقبول. ذوبان قمم الميتفورمين كان مرئيا في DSC–حراري من السواغات المخدرات خليط، مشيرا 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 (HPMC وPEO) وتورم محسن (SSG). تبين أن صياغة مع تركيز البوليمر 250 ملغ، 60 ملغ $NaHCO_3$، و50 SSG ملغ الوفاء requistes 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 سريعا وخطية للعسل 2 ساعة، إلا أنه انخفض بعد ذلك وحافظت على الخطي حتى 8 ساعات. . يسمح الجمع بين HPMC وPEO مراقبة فعالة من الافراج عن المخدرات لمدة 12 ساعة. أظهر الرقم SEM طبيعة غير قابلة للاختراق من قرص السطح الخارجي وقليلا 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 أيضا أن الافراج عن المخدرات يحدث من قبل نشرها. استنادا إلى دراسة الاستقرار تسارع؛ وجد صياغة الأمثل لتكون مستقرة لمدة ثلاثة أشهر دون أي تغييرات كبيرة في الفحص، لمحة 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).

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Siti Hadijah Shamsudin
Dean, Kulliyyah 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.

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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 Kulliyyah 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. Dzadil, 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.

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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

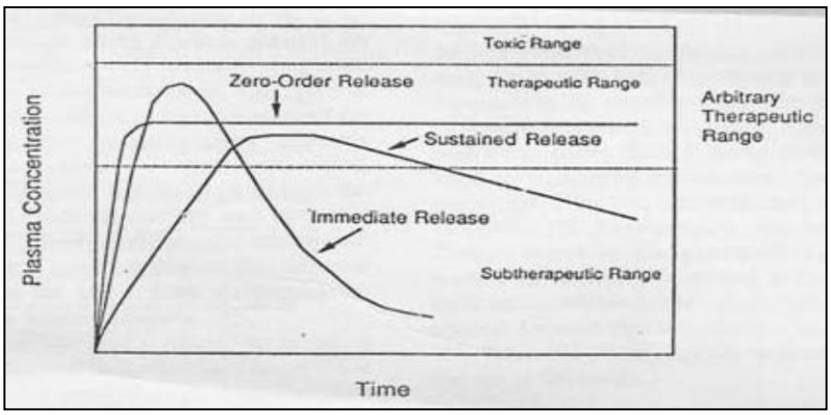

Figure 1.1. Differences among various drug release profile (Narang, 2011)

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.

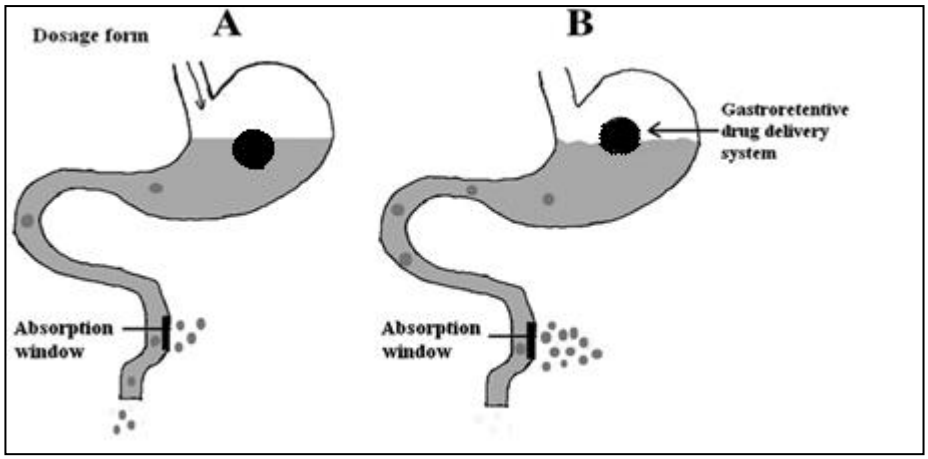

Figure 1.2. Drug absorption in: (A) conventional dosage form and (B) the gastroretentive drug delivery system (Kumar & Philip, 2007)

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).