



**DEVELOPMENT, SCALE UP, PHARMACOKINETIC
AND PHARMACODYNAMIC EVALUATION OF
MODIFIED RELEASE GLICLAZIDE 60 MG TABLET
FORMULATION PRODUCED BY DIRECT
COMPRESSION**

BY

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ABSTRACT

Background: Gliclazide modified release (MR) tablets are available as innovator brand but it is expensive. It is produced by wet granulation using maltodextrin syrup. Direct compression has the advantage of less processing steps, avoiding degradation of heat and moisture sensitive drugs and reduction of production cost and time. Several factors may affect drug release from MR tablets including the type of polymers and excipients used, their particle size and viscosity grade. Segregation is a common problem encountered during tablet manufacturing by direct compression which makes scale up challenging. Careful selection of excipients is required to avoid this problem. Description of degradation profile of gliclazide in MR tablets is lacking in literature. **Objectives:** To study factors affecting gliclazide release from tablet formulation in order to successfully develop a modified release gliclazide 60 mg tablet formulation produced by direct compression. Also, to scale up and evaluate stability and bioequivalence of the developed formulation compared to the reference product. **Methodology:** The effect of different hydrophilic and hydrophobic drug retaining polymers and excipients on gliclazide release was studied. Central composite design was used to study the effect of Methocel[®] and Maltrin[®] content on gliclazide release. An optimum formula was selected and a 10,000 tablets batch was produced in IKOP Sdn. Bhd. Stability of the produced tablets were tested according to ASEAN Guidelines on Stability Study of Drug Product. A pilot bioequivalence study was conducted to generate a preliminary data on the *in vivo* pharmacokinetics of the developed tablet formulation. **Results and Discussion:** Increasing drug retaining polymer in the tablet resulted in less gliclazide release. The release is slower the higher the viscosity grade or hydrophobicity of the drug retaining polymer. Water insoluble fillers resulted in more controlled release compared to water soluble ones. More significant effect of gliclazide release was associated with maltodextrin particle size compared to molecular size. It was possible to obtain the target gliclazide release profile with the use of Methocel[®] K100 LV DC2, Supertab[®] 11 SD and Maltrin[®] M150 in the tablet formulation. The optimized formulation showed an 80% similarity and 3% difference in dissolution profile when compared to the branded one (Diamicon[®] MR 60 mg tablet). Increasing Methocel[®] content reduced gliclazide release at all the time points while Maltrin[®] M150 exerted a release slowing effect in the first 3 h and release enhancing thereafter. A scale up batch that conforms to compendial requirements of assay, content uniformity and friability, in addition to a dissolution profile within the target was successfully produced. The optimized formulation was stable during a six months accelerated stability study. It showed little change during this storage period and the degradation rate was 0.58% of the labelled content. The dissolution profile also showed little change during this storage period. Impurity A is the major degradation product in the optimized tablet formulation. A pilot study to compare the biopharmaceutical performance of the optimized formulation with the branded product showed close values of pharmacokinetic parameters of both developed and branded formulations. The generic to branded ratios were 1.04, 0.93 and 0.93 for the C_{max} , AUC_{0-t} and $AUC_{0-\infty}$, respectively. **Conclusion:** The developed prototype formulation showed a good stability, *in vitro* dissolution and *in vivo* performance similarity with the branded formulation. Further evaluation is required in order to commercialize this generic formulation.

خلاصة البحث

يتوفر عقار غليكلازايد حالياً على شكل اقراص ممتدة المفعول تتناول مرة واحدة يوميا ولكنها مكلفة و يتم انتاجها بواسطة التحبيب الرطب باستخدام شراب المالتودكسترين. تمتاز طريقة الضغط المباشر بخطوات تصنيع اقل مع تجنب تحلل العقاقير الحساسة للحرارة والرطوبة, بالإضافة الى تقليل وقت وتكلفة الانتاج. تؤثر العديد من العوامل في اطلاق العقار من الاقراص ممتدة المفعول مثل نوع البوليمرات و الصواغات المستخدمة وكذلك حجم الحبيبات ودرجة اللزوجة. تعد انفصال المكونات من المشكلات الشائعة لطريقة الضغط المباشر مما يجعل استخدامها تحدياً كبيراً ومن الواجب اختيار الصواغات بعناية لتجنبها. لا تحتوي الابحاث المنشورة على معلومات بخصوص نواتج تحلل الجليكلازايد في الحبوب ممتدة المفعول. يهدف هذا البحث الى دراسة العوامل المؤثرة على اطلاق الجليكلازايد من الحبوب ممتدة المفعول من اجل تطوير اقراص بقوة 60 مجم و انتاجها بطريقة الضغط المباشر بشكل صناعي وتقييم ثباتها وتكافؤها الحيوي مع المنتج الأصلي. في سبيل ذلك تم اختبار تأثير انواع مختلفة من البوليمرات المحبة او الكارهة للماء والصواغات. كما استخدمت طريقة التصميم المركب المركزي لدراسة تأثير الميثوسل والمالترين على اطلاق الغليكلازايد و تم انتاج تشغيلة بحجم عشرة الاف قرص ودراسة ثباتها تبعاً لارشادات الاسيان وكذلك دراسة تكافؤها الحيوي مع المنتج الأصلي. تبين من الدراسة ان زيادة محتوى الاقراص من البوليمر وزيادة لزوجته واستخدام الصواغات التي لا تذوب في الماء يؤدي الى خفض إطلاق غليكلازايد. يؤدي زيادة محتوى الاقراص من الميثوسل الى انخفاض اطلاق الجليكلازايد في كل نقطة زمنية داخل المختبر في حين يؤدي زيادة المحتوى من المالترين الى تباطؤه في الثلاث ساعات الاولى وزيادته بعد ذلك. وقد تم التوصل لصيغة مثلى لاقراص غليكلازايد ممتدة المفعول تميزت بالتوافق مع متطلبات دستور الادوية من حيث المحتوى من المادة الفعالة وتوحيد المحتوى والتفتت، مع اطلاق للدواء بمعدل تشابه 80% و فرق 3% مقارنة مع الاقراص صاحبة العلامة التجارية. تم انتاج تشغيلة بحجم عشرة الاف قرص في مصنع الادوية IKOP أظهرت صياغة مستقرة أثناء دراسة الثبات المسرع تحت درجة حرارة 40 مئوية لمدة ستة أشهر حيث تناقصت المادة الفعالة بمعدل 0.58% مع تغير طفيف في اطلاق الدواء. وأظهرت دراسة لمقارنة أداء الاقراص الحيوي بالمقارنة مع المنتج ذو العلامة التجارية تقارب المعاملات الدوائية لكلا المنتجين. كانت النسبة 1.04، 0.93 و 0.93 ل C_{max} ، AUC_{0-t} و $AUC_{0-\infty}$ ، على التوالي. مما سبق يتبين ان الصيغة النهائية لاقراص غليكلازايد ممتدة المفعول التي تم تطويرها من خلال هذا البحث قد أظهرت ثباتاً جيداً، و تشابه اطلاقها للدواء في المختبر وفي جسم الانسان مع الاقراص ذات العلامات التجارية، وبالتالي يمكن انتاجها بشكل تجاري اذا اجريت الدراسات المطلوبة.

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DECLARATION

I hereby declare that this thesis is the result of my own investigations, 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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Firstly, praise and thanks be to Allah that bestowed upon us countless blessings and without him no work would be accomplished.

وَمَا بِكُمْ مِّن نِّعْمَةٍ مِّنَ اللَّهِ ۖ ثُمَّ إِذَا مَسَّكُمُ الضُّرُّ فَإِلَيْهِ تَجَاوَرُونَ

And whatever you have of favour - it is from Allah. Then when adversity touches you, to Him you cry for help.

(Surah An-Nahl: 53)

Among his blessing during this journey is to have supporting supervisors, family, colleagues and administration.

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LIST OF ABBREVIATIONS

ACN	Acetonitrile
Alu	Aluminium
API	Active pharmaceutical ingredient
BCS	Biopharmaceutical Classification System
BMR	Batch manufacturing record
BP	British Pharmacopoeia
CCD	Central composite design
CMC	Carboxymethyl cellulose
Conc.	Concentration
CV	Coefficient of variation
DC	Direct compression
DCP	Dibasic calcium phosphate
DSC	Differential scanning calorimetry
EC	Ethyl cellulose
ESI	Electrospray ionization
FDA	Federal Drug Authority
FTIR	Fourier transform infrared spectroscopy
GLZ	Gliclazide
h	Hour
HPC	Hydroxypropyl cellulose
HPLC	High performance liquid chromatography
HPMC	Hydroxypropyl methylcellulose, hypromellose
HR	Heart Rate
IREC	IIUM Research Ethics Committee
IS	Internal standard
LCMS	Liquid Chromatography-Mass Spectrometry
m/z	Mass-to-charge ratio
MR	Modified Release
MRM	Multiple reaction monitoring
MRT	Mean release time
MS	Mass spectrometer
MSE	Mean square error
PCL	Poly- ϵ -caprolactone
PM	Poor metabolisers
PVA	Polyvinyl alcohol
PVDC	Polyvinylidene chloride
PVP	Polyvinyl Pyrrolidone
RH	Relative humidity
RS	Reference standard
RSD	Relative standard deviation
RSM	Response surface methodology
SD	Standard deviation
SU	Sulphonylurea
TPP	Triphosphate
UHQ	Ultra-high quality