# 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 (Diamicron® 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 حاليا 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, بالاضافة 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 تحديا كبيرا ومن الواجب اختيار الصواغات بعناية لتجنبها. لا تحتوي الابحاث المنشورة على معلومات بخصوص نواتج تحلل الجليكلازيد في الحبوب ممتدة المفعول. يهدف هذا البحث الى دراسة العوامل المؤثرة على اطلاق الجليكلازيد من الحبوب ممتده المفعول من اجل تطوير اقراص بقوة 60 مجم و انتاجها بطريقة الضغط المباشر بشكل صناعى 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 تبعا 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 الجليكلازيد 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 غليكلازيد ممتدة المفعول تميزت بالتوافق مع متطلبات دستور الادوية من حيث المحتوى من المادة الفعالة وتوحيد المحتوى والتفتت، مع اطلاق للدواء بمعدل تشابه 80٪ وفرق 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 مؤية 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 غليكلازيد 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.

# APPROVAL PAGE

The thesis of Tarek Mohamed Ali Elsayed has been approved by the following:

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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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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)

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| | |
|---|---|
| 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 Pyrrolidine |
| RH | Relative humidity |
| RS | Reference standard |
| RSD | Relative standard deviation |
| RSM | Response surface methodology |
| SD | Standard deviation |
| SU | Sulphonylurea |
| TPP | Tripolyphosphate |
| UHQ | Ultra-high quality |