DEVELOPMENT OF A FIXED-DOSE COMBINATION CAPSULE OF CARBAMAZEPINE AND GABAPENTIN

BY

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ABSTRACT

The rate of patient's compliance is markedly reduced as the number of medications and dosing frequency increased. The compliance for the combination of carbamazepine tablet which is twice daily dosing and gabapentin capsule which is given three times daily is greatly affected in painful diabetic peripheral neuropathy patient. This study aim to develop a fixed-dose combination of carbamazepine and gabapentin (FDC CBZ-GBP) in order to simplify the treatment and improve the compliance. Hence, it is important to identify the compatible excipient for both drugs for the purpose of formulation development. Compatibility study was performed on both active pharmaceutical ingredients (API) and each API with several excipients using differential scanning calorimetry (DSC) and supported by attenuated total reflectance-fourier transform infrared spectroscopy (ATR-FTIR). DSC results showed incompatibility between GBP and CBZ, lactose monohydrate, magnesium stearate, talc and hydroxylpropyl methylcellulose where the melting peak of GBP significantly shifted. However, ATR spectra of those combinations excluded these incompatibilities. Preliminary lab scale production of FDC CBZ-GBP for 2 kilograms was done with the incorporation of 2 excipients only; namely, lactose and magnesium stearate. The lab scale FDC CBZ-GBP had flow function > 10, compressibility index 11.73±2.28% and Hausner ratio 1.13 ± 0.03 which indicated free-flowing powder. Thus, the intended fill weight of 300 mg ± 7.5% can be achieved. The analytical method development (AMD) and analytical method validation (AMV) of FDC CBZ-GBP including specificity, accuracy, precision, intermediate precision, linearity, limit of detection (LOD) and limit of quantification (LOQ) were performed by using HPLC. All the AMV parameters met all the compendial specifications. FDC CBZ-GBP was scaled-up to 24 kilograms to identify optimum processing parameters such as mixing time, mixing direction, dosator speed and dose controller. Based on scale-up results, the optimum mixing time was 52.5 min with 4 clockwise and 2 anticlockwise turns. The expected setting of dosator speed (400 pcs/min) and dose controller (15 mm) for capsule filling process was not stable because process capability index (Cpk) was less than 1. Samples from scale-up process were taken and stored in both real time and accelerated stability chambers for stability study. All stability study parameters including moisture content, assay of carbamazepine and gabapentin, disintegration time and dissolution profile at all-time points met the compendial specifications. In conclusion, FDC CBZ-GBP was successfully developed into a new dosage form of a fixed-dose capsule.

خلاصة البحث

إن معدل التزام المرضى قد تناقص بشكل ملحوظ بزيادة عدد الادوية وعدد الجرعات. الالتزام في اخذ مزيج من حبوب carbamazepine التي تؤخذ مرتين في اليوم وكبسولات gabapentin التي تؤخذ ثلاث مرات يوميا قد تأثر كثيرا عند مرضى اعتلال الاعصاب المحيطية السكري شديد الألم. هذه الدراسة تطمح الى تطوير جرعة ثابتة من مزيج carbamazepine و gabapentin (FDC CBZ-GBP) من اجل تبسيط العلاج وتحسين الالتزام. بالتالي فمن المهم تمييز السواغات المتوافقة لكلا الدوائيين لغرض تطوير التركيبة. تم تنفيذ دراسة التوافق على المكونات الصيدلية الفعالة API لكلا الدوائيين ولكل السواغات باستخدام المسح الحراري التفاضلي DSC ومدعم ب مطيافية الاشعة تحت الحمراء (ATR-FTIR). نتائج DSC أظهرت عدم توافق بين GBP و CBZ, lactose monohydrate, magnesium stearate, talc و hydroxylpropyl methylcellulose حيث أن ذروة درجة الانصهار ل GBP قد ازيحت بشكل ملحوظ. ومع ذلك فإن أطياف ATR لتلك التركيبات تستبعد وجود عدم التوافق. النتائج المخبرية الأولية ل FDC CBZ-GBP ل 2 كيلوجرامات قد تمت مع دمج سواغين هما, lactose and magnesium stearate, فقط. قياس الانسيابية كان اقل من 10 و compressibility index , 11.73±2.28% and Hausner ratio 1.13 ± 0.03 والذي يشير الى انسيابية حرة للمسحوق. وهكذا فإن وزن التحميل المطلوب ل 300 ملجم ± 7.5 % يمكن تحقيقه. تطوير والتحقق من طريقة التحليل والتي تشمل عدة عوامل كالخطية والدقة وغيرها قد تمت باستخدام HPLC. جميع المعايير استوفت جميع المواصفات الدستورية. تم توسيع الإنتاج الى 24 كجم من اجل تحديد معايير المعالجة المثلى مثل مدة الخلط, اتجاه الخلط ومعاملات آلة التعبئة في الكبسولات. وفقا للنتائج فإن وقت الخلط الأمثل كان 52.5 دقائق مع 4 دورات مع عقارب الساعة ودورتين عكسها. الإعدادات المتوقعة للتعبئة بسرعة 400 كبسولة في الدقيقة ومعامل 15 للالة من اجل عملية ملء الكبسولة لم تكن مستقرة لأن Cpk اقل من 1. تم أخذ عينات من عملية توسيع النطاق وتم حفظها في غرف دراسة الثباتية المسرعة والحقيقية. جميع خصائص دراسة الاستقرار والتي تشمل محتوى الرطوبة, فحص carbamazepine و gabapentin, وقت التفكك و الانحلالية في جميع الأوقات استوفت جميع المواصفات الدستوري . في الختام, تم بنجاح تطوير شكل جرعة جديد من كبسولات ثابتة الجرعة ل FDC CBZ-GBP .

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 in Pharmaceutical Sciences (Pharmaceutical Technology).

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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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LIST OF EQUATIONS

LIST OF ABBREVIATIONS

ACC	Accelerated
ACN	Acetonitrile
ACW	Anti-clockwise
AMD	Analytical Method Development
AMV	Analytical Method Validation
AOR	Angle of Repose
API	Active Pharmaceutical Ingredient
ATR-FTIR	Attenuated Total Reflectance Fourier-Transform Infrared Spectroscopy
AWP	Average Wholesale Price
BBB	Blood Brain Barrier
BCAA	Branched-Chain Amino Acids
BCAA-T	Branched-Chain Amino Acids Transferase
BCS	Biopharmaceutical Classification System
BP	British Pharmacopeia
CBZ	Carbamazepine
CI	Carr Index/ Compressibility Index
CNS	Central Nervous System
CPP	Critical Process Parameters
CQA	Critical Quality Attributes
CSH	Corn starch
CW	Clockwise
DRESS	Drug Rash with Eosinophilia and Systemic Symptoms
DSC	Differential Scanning Calorimetry
FDC	Fixed-Dose Combination
FDC CBZ-GBP	Fixed-Dose Combination of Carbamazepine and Gabapentin
ffc	Flow Function Coefficient
FTIR	Fourier-Transform Infrared Spectroscopy
GABA	γ-aminobutyric acid
GBP	Gabapentin
GC	Gas Chromatography
HCl	Hydrochloric acid
HPLC	High Performance Liquid Chromatography
HPMC	Hydroxylpropyl methylcellulose
HR	Hausner ratio
ICH	International Council on Harmonisation
LAC	Lactose monohydrate
LOD	Limit of Detection

LOQ	Limit of Quantification
MAS	Magnesium stearate
MCC	Microcrystalline cellulose
NaOH	Sodium hydroxide
PDPN	Painful Diabetic Peripheral Neuropathy
PPI	Peak Purity Index
PXRD	Powder X-ray Diffraction
QTPP	Quality Target Product Profile
RH	Relative Humidity
RSD	Relative Standard Deviation
RT	Real-time
SD	Standard Deviation
SEM	Scanning Electron Microscopy
TALC	Talc
TDM	Therapeutic Drug Monitoring
TEN	Toxic Epidermal Necrolysis
TG/DTG	Thermo-Gravimetry/Derivative Thermogravimetry
US FDA	United States Food and Drug Administration
USP	United States Pharmacopeia
UV	Ultraviolet
WS	Working standard

CHAPTER ONE

INTRODUCTION

1.1 BACKGROUND OF THE STUDY

Gabapentin (GBP) was first synthesized by Gerhard Satzinger in 1974. It was categorized under biopharmaceutical classification system (BCS) class III (Papich & Martinez, 2015). It was approved by United States Food and Drug Administration (US FDA) in 2002 for nerve-related pain treatment (Kamerman et al., 2016). It has been recommended as one of the first line drugs (Figure 1.1) in the management of peripheral diabetic neuropathy as stated in Malaysia clinical practice guideline (Vijayan et al., 2012). According to the studies conducted in China (Wang et al., 2016), Greece (Athanasakis et al., 2013) and Spain (Rodríguez et al., 2007), pregabalin is more cost-effective than gabapentin for treatment of painful diabetic peripheral neuropathy (PDPN). However, the average wholesale price (AWP) for pregabalin is almost 40-fold higher than gabapentin (Cohen et al., 2015). Therefore, gabapentin remains the drug of choice for PDPN in Malaysia and the tenth most prescribed medication in United States.

Painful diabetic peripheral neuropathy (PDPN) is one of the complications for chronic diabetic patients (Juster-Switlyk & Smith, 2016). The symptoms can be debilitating to the extent that it can cause anxiety, sleep disturbances and reduce mobility (Javed, Alam & Malik, 2015). The treatment management is often challenging and adding up to the number of drugs being taken by chronic diabetic patients. They are usually been prescribed with a number of drugs to treat multiple complications associated with microvascular and macrovascular diseases (Chawla, Chawla & Jaggi, 2016). These treatment complexity could decrease patients' compliance as the number

of drugs and daily doses increase (J. Jin et al., 2008). Therefore, compliance issue due to multiple dosing and polypharmacy attributed to chronic diabetic patient can be minimized by introducing a fixed-dose combination (FDC) of two drugs as shown in Table 1.1.

Most guidelines recommended monotherapy as the first line treatment for neuropathic pain. The examples of drug classes that have consistently shown efficacy against PDPN are anticonvulsants, antidepressants, opioids and local anesthetics. The latest study of PDPN pathophysiology suggested that targeting central and peripheral nervous system simultaneously can improve treatment outcome (Eisenberg & Suzan, 2014). Thus, we hypothesize that combination of two drugs that can bind to the different receptors located at central and peripheral regions may demonstrate better pain relief due to synergistic effect. It was reported earlier in previous study that, the combination of gabapentin and morphine resulted in better analgesia effect at lower doses compared to when given individually (Gilron et al., 2005). However, constipation, sedation, and dry mouth were reported in the subjects. Additionally, the risk of respiratory depression was presented when opioid was given in combination with gabapentin (Kumar et al., 2016). Therefore, the combination of gabapentin and opioid is no longer preferred.

The recent research on the synergistic effect of gabapentin and carbamazepine could be an alternative against trigeminal neuralgia (Matsumoto et al., 2015) and PDPN (Al-Mahmood et al., 2016). In addition, no dosage adjustment and no pharmacokinetic interaction was reported when gabapentin was combined with carbamazepine (Radulovic et al., 1994). Therefore, the idea of combining carbamazepine and gabapentin in one dosage form would be a promising approach to simplify the regime and anticipated to improve patient compliance to the treatment regimen.