UNIVERSITI PUTRA MALAYSIA

DETERMINATION OF AMOXICILLIN CROSS-CONTAMINATION IN IBUPROFEN TABLETS USING ULTRA PERFORMANCE LIQUID CHROMATOGRAPHY AND IDEXX SNAP KIT

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May 2017

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Penicillin is one of the most effective β-lactam antibiotics against bacterial infections. Nevertheless, the allergic reactions associated with the usage of penicillin ranges from rashes to life-threatening anaphylaxis. Hence, the regulations imposed the pharmaceutical manufacturers to implement strict controls during the production process compels these manufacturers to test non-penicillin drug products for traces of penicillin in which the possibility of exposure to cross-contamination exists. Furthermore, the United States Food and Drug Administration (USFDA) prohibit the marketing of such products if detectable penicillin levels are found. In-depth investigations revealed a real need for an analytical technique, with appropriate detection level, that can determine the presence of penicillin in non-penicillin medicines.

The intent of this study was to develop, optimize, and validate two analytical methods for determination of the amoxicillin as a β-lactam penicillin contaminant in ibuprofen tablets 400 mg using ultra performance liquid chromatography (UPLC) and Idexx SNAP® β-lactam test kits. In the first case, a novel quantitative analytical method was developed and validated using UPLC. Extraction of amoxicillin was done in double-distilled water, and separation of the different compounds was achieved using a bridged ethylene hybrid (BEH) C18 column with a particle size of 1.7 µm (100 mm × 2.1 mm). The isocratic run was accomplished using phosphate buffer (pH=5.0) : methanol (95:5, v/v) as mobile phase at a flow rate of 0.3 ml/min. The specificity and accuracy of the method proved to be suitable within the requirements of the current Good Manufacturing Practices (cGMP) for finished pharmaceuticals. The developed method was validated according to the International Conference on Harmonization (ICH) guidelines Q2 (R1). The

method was linear in the range of 24 to 96 µg/l for amoxicillin with a correlation coefficient r = 0.999. The lowest detection limit of amoxicillin was found to be of 0.008 µg/ml. The recovery data was found to be in the range of 97.6% to 101.7%. The precision was assessed in terms of injection repeatability with the maximum relative standard deviation (RSD) of 1.8%. Highly reproducible results with RSD of 1.97% were obtained for a series of measurements of the analyte in two different days. Applying the developed UPLC method will enhance the approval process in the pharmaceutical industry significantly. In the second study, a qualitative screening method for determination of cross-contamination of amoxicillin in ibuprofen tablets 400mg using Idexx SNAP® β-lactam test kits was optimized and validated. The kit is one of the USFDA approved biosensors that is used for detection of β–lactam antibiotics in milk samples. It was established based on an enzyme-linked, receptor binding assay mechanism. The method was validated according to the European Commission Decision 2002/657/EC, and satisfactory results were obtained for its performance characteristics. Twenty (20) negative controls and 20 positive samples revealed that the method was specific with no false-compliant results. The detection limit (DL) of amoxicillin proved to be below the USFDA established a safe level of 10 parts per billion (ppb) with a total assay time of 10 minutes. In a variety of matrices, the method was applied to 13 different oral solid pharmaceutical products with a maximum negative reading of 0.88 and minimum positive reading of 1.31. The ruggedness of the method was confirmed through the design of experiment (DOE) approach in which 1/16 fractional factorial design was constructed using Minitab software to obtain maximum information from the least amount of experimental runs. In general, both of the UPLC and Idexx SNAP® screening methods were able to detect the amoxicillin in the ibuprofen tablets at the safe level and can be applied successfully in pharmaceutical quality control laboratory to fulfill the regulatory requirements.

Abstrak tesis yang dikemukakan kepada Senat Universiti Putra Malaysia sebagai memenuhi keperluan untuk Ijazah Doktor Falsafah

PENENTUAN KONTAMINASI SILANG AMOXISILIN DALAM IBUPROFEN MENGGUNAKAN KROMATOGRAFI CECAIR PRESTASI ULTRA DAN KIT SNAP IDEXX

Oleh

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Penisilin merupakan salah satu antibiotic β-laktam yang paling efektif terhadap infeksi bakteria. Walau bagaimanapun, reaksi alergi yang berkaitan dengan penggunaan penisilin meliputi dari ruam hingga anafilaksis yang mengancam nyawa. Oleh sebab itu, peraturan yang dikenakan terhadap pengeluar farmaseutikal bagi melaksanakan kawalan yang ketat ketika pengeluaran memaksa mereka untuk menguji produk ubat bukan penisilin bagi surih penisilin yang berkemungkinan terdedah kepada wujudnya pencemaran silang. Tambahan pula, Pentadbiran Makanan dan Ubatan Amerika Syarikat (USFDA) menyekat pemasaran produk tersebut sekiranya tahap pengesanan penisilin dijumpai. Kajian analisis diperjelaskan secara mendalam untuk menentukan tahap pengesanan yang membolehkan pengesanan kehadiran penicilin di dalam ubat tanpa penicilin.

Tujuan kajian ini adalah untuk membangunkan, mengoptimumkan dan mengesahkan dua kaedah analitikal bagi penentuan amoxisilin sebagai pencemar penesilin β-laktam dalam tablet ibuprofen 400 mg menggunakan kromatografi cecair prestasi ultra (UPLC) dan kit ujian β-laktam Idexx SNAP®. Dalam kes pertama, kaedah analitikal kuantitatif yang novel telah dibangun dan disahkan menggunakan UPLC. Ekstrasi Amoxisilin telah dijalankan dalam air dwisuling, dan pengasingan kompaun yang berbeza menggunakan kolum C18 hibrid etilin titian (BEH) dengan saiz partikel 1.7 µm (100 mm × 2.1 mm). Jalanan isokratik tercapai menggunakan bufer fosfat (pH=5.0) : metanol (95:5, v/v) sebagai fasa bergerak pada kadar alir 0.3 ml/min. Spesifisiti dan ketepatan kaedah terbukti sesuai dari segi kehendak Amalan Pengeluaran Berkesan Semasa (cGMP) bagi farmaseutikal siap. Kaedah yang dibangunkan telah divalidasikan berdasarkan garis panduan Q2(R1) International Conference on Harmonization (ICH). Kaedah tersebut adalah linear dalam lingkungan 24 hingga 96 µg/l bagi amoxisilin dengan

korelasi pekali r = 0.999. Terendah batas pengesanan untuk amoxisilin didapati pada lingkungan 0.008 µg/ml. Perolehan data didapati pada lingkungan 97.6 hingga 101.7%. Ketepatan telah dinilai dari segi pengulangan suntikan dengan maksimum deviasi standard relatif (RSD) 1.8%. Hasil boleh ulang semula yang tinggi dengan RSD 1.97% telah diperoleh bagi siri pengukuran analit dalam dua hari yang berbeza. Mengaplikasikan kaedah yang membangun ini dapat meningkatkan secara signifikan kelulusan proses dalam industri farmaseutikal. Dalam kajian kedua, kaedah saringan kualitatif bagi penentuan kontaminasi silang amoxisilin dalam tablet ibuprofen 400mg menggunakan kit ujian β-laktam Idexx SNAP®. telah dioptimum dan disahkan. Kit ini merupakan salah satu biosensor sah USFDA yang digunakan untuk mengesan antibiotik β-laktam dalam sampel susu. Dapatan ini berdasarkan mekanisma cerakinan pengikat reseptor pautan enzim. Kaedah tersebut telah disahkan berdasarkan Keputusan Suruhanjaya Eropah 2002/657/EC dan dapatan yang memuaskan diperoleh bagi ciri prestasinya. Dua puluh (20) kawalan negatif dan dua puluh (20) sampel positif menunjukkan bahawa kaedah tersebut adalah spesifik tanpa dapatan kepatuhan palsu. Had pengesanan (DL) amoxisilin dibuktikan berada di bawah USFDA yang dikira tahap selamat bagi 10 bahagian par bilion (ppb) dengan jumlah masa cerakinan 10 minit. . Dalam pelbagai matrik, kaedah tersebut telah diaplikasikan pada 13 produk farmaseutikal pepejal oral yang berbeza dengan pembacaan negatif maksimum 0.88 dan pembacaan positif minimum 1.31. Kelasakan kaedah telah terbukti melalui reka bentuk pendekatan eksperimen (DOE) yang mana 1/16 reka bentuk faktorial fraksional telah dibina menggunakan perisian Minitab untuk mendapatkan maklumat maksimum daripada jumlah jalanan eksperimen paling kurang.

Secara umumnya, kedua-dua UPLC dan kaedah saringan SNAP Idexx bagi penentuan amoxisilin dalam tablet ibuprofen 400 mg dibuktikan berada di bawah USFDA yang dikira tahap selamat bagi 10 bahagian par bilion (ppb) dan telah berjaya diaplikasikan pada makmal kawalan kualiti farmaseutikal dan memenuhi keperluan peraturan.

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I certify that a Thesis Examination Committee has met on 22 May 2017 to conduct the final examination of Mohamed Ali Mohamed Ali on his thesis entitled "Determination of Amoxicillin Cross-Contamination in Ibuprofen Tablets using Ultra Performance Liquid Chromatography and IDEXX Snap Kit" in accordance with the Universities and University Colleges Act 1971 and the Constitution of the Universiti Putra Malaysia [P.U.(A) 106] 15 March 1998. The Committee recommends that the student be awarded the Doctor of Philosophy.

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LIST OF ABBREVIATIONS

A	Eddy diffusion term (Multipath term)
ANOVA	Analysis of variance
AOAC	Association of analytical communities
AU	Absorbance unit
B	Longitudinal diffusion term
BAW	Bulk acoustic wave
BEH	Bridged ethylene hybrid
BSM	Binary solvent manager
C	Mass transfer term for mobile and stationary phases
CCβ	Detection capability
CMO	Contract manufacturing organizations
C6	Hexyl carbon chain
C8	Octyl carbon chain
C18	Octadecyl carbon chain
cGMP	Current good manufacturing practices
D_m	Solute's diffusion coefficient in the mobile phase
D_s	Solute's diffusion coefficient in the stationary phase
DL	Detection limit
DOE	Design of experiment
d_c	the column's diameter
d_f	Thickness of the stationary phase
d_p	Average diameter of the particulate packing material
EC	European Commission
EMA	European medicines agency
EP	European Pharmacopeia
EPA	Environmental Protection Agency
FDA	Food and drug administration
FR	Flow rate

f_n	function of
F_{opt}	Optimum flow
GDP	Good documentation practices
GMP	Good manufacturing practices
GOx	Glucose oxidase
HETP / H	Height equivalent to the theoretical plate
HILIC	Hydrophilic interaction liquid chromatography
HPLC	High-performance liquid chromatography
HRP	Horse radish peroxidase
HSS	High strengthen silica
H_m	Contributions of mass transfer in the mobile phase
H_p	Height of a theoretical plate
H_s	Contributions of mass transfer in the stationary phase
ID	Internal dimension
ICH	International conference on harmonization
IUPAC	International union of pure and applied chemistry
ISO	International Organization for Standardization
K	Retention factor or Capacity factor
LPS	Lipopolysaccharide
MS	Mass spectrometry
N	Theoretical plate number
NF	National formulary
nm	nanometer
NSAID	Nonsteroidal anti-inflammatory drug
OFAT	One-factor-at-a-time
OOS	Out-of-specification
PDA	Photodiode array detector
pH	A measure of the hydrogen ion concentration of a solution
PBP	Penicillin-binding protein
ppb	Part per billion

psi	pound per square inch
QL	Quantitation limit
q	constant related to the column packing material
RCRA	Resource conservation and recovery act
RP	Reverse phase
RS	Reference standard
RSD	Relative standard deviation
RT	Retention time
Rs	Resolution
S	Slope of the calibration curve
SAW	Surface acoustic wave
SD	Standard deviation
SERS	Surfaced-enhanced raman substrate
SPR	Surface plasmon resonance
SQT	System qualification test
T	Tailing factor
TUV	Tunable Ultraviolet
USP	United States Pharmacopeia
UPLC	Ultra-performance liquid chromatography
u	Linear velocity of the mobile phase
V	Retention volume
Vis	Visible
V_0	Void volume
v/v	Volume / volume
W	Peak width
WHO	Word health organization
°C	Degrees Celsius
α	Selectivity or Separation factor
γ	Constant related to the efficiency of column packing
σ	Standard deviation of the response

φ	Constant accounts for the consistency of the column packing

CHAPTER 1

INTRODUCTION

1.1 Research Background

Penicillin is β-lactam antibiotic that used for the treatment of many different bacterial infections, usually caused by Gram-positive organisms (Sweetman, 2014). On the contrary, it could be one of the most common resources for potential allergic reaction to 1 – 10% of the populations (Center, 2014). Non-penicillin drug products that are cross-contaminated with penicillin may initiate the same type of hypersensitivity reactions that penicillins can trigger, including life-threatening anaphylactic shock. the In this regard, the regulatory bodies set different guidelines to prevent cross-contamination and the adverse effect of medicinal products intended for human and veterinary use (Commission, 2015a, 2015b; NRP, 2013). In Pharmaceutical Industry, the regulatory bodies moved towards keeping the manufacturing of penicillin and non-penicillin-based drugs separate over the last 40 years. The control procedures include the dedicated utility in the manufacturing of the API (ICH, 2000), facility design, process equipment (USFDA, 2015a), Ventilation, air filtration, air heating and cooling system (USFDA, 2015b). Further guidelines require the same type of separation for non-penicillin β-lactam antibiotics (USFDA, 2013). Even with the continuous effort, the entire separation was not achieved, and obviously, the risk still exists for cross-contamination of penicillin to non-penicillin drug products.

Additionally, USFDA guidelines 21 CFR 211.176 (USFDA, 2015c) requires manufacturers to test non-penicillin drug products for penicillin content where the possibility of exposure to cross-contamination exists and prohibits manufacturers from marketing such products if detectable levels of penicillin are found. Over the past few years, the analytical procedures that deal with antibiotics contaminants detection have been focused on edible products. Different methods were reported for determination of antibiotics residue in milk samples (Díaz-Bao *et al*., 2015; Tona & Olusola, 2014), food from animal origins (Jabbar & Rehman, 2013) and animal tissues (Samanidou *et al.*, 2007).

In the pharmaceutical sector, most of the analytical methods reported for determination of trace amounts of penicillin have been directed to cleaning validation samples (Narendra *et al*., 2009; Trivedi *et al*., 2013). In November 1977, the USFDA reported a method for the detection of penicillin in drugs (Carter, 1977) using a bioassay method, but this analytical methodology was time-consuming, limited to the detection of Penicillin G and ampicillin and does not include other β-lactam antibiotics. Thereafter, only one method was reported for determination of penicillin in non-penicillin drug products using

HPLC (High Pressure Liquid Chromatography) coupled with Tandem Mass Spectrometry (Akada et al., 2005). The drawback of the method was the limitation of the detection to Amoxicillin, Ampicillin, and Flucloxacillin in Funguard lyophilized drug product and the detection limit was 30 ppb which is higher than the safe level set by the regulatory (USFDA, 1997).

Since then; it has been clear that the development of new analytical procedures for detection of penicillin residues has not kept pace with the development with new drugs. Therefore, real need for an analytical method for the detection of residues of the β-lactam antibiotics as contaminants still exist. The prerequisite for the method that it is fast and capable of detecting the target analyte at the tolerance/ safe level (10 ppb) established by the USFDA (USFDA, 2005; 2011).

1.2 Problem Statement

In multi-products drug manufacturing plants, the possibility of penicillin cross-contamination to other non-penicillin products is existed due to movement of the people, equipment, and materials. This type of cross-contamination presents great risks to patient safety, including anaphylaxis and death (More, 2014).The allergic reaction to penicillin that has been shown by 10% of the world population (Miller, 2002; Warrington & Silviu-dan, 2011) attracted the attention of different regulatory agencies, specifically the USFDA, to establish strict regulations to avoid cross-contamination of penicillin with non-penicillin medicines (USFDA, 2015a, 2015b).

The potential hazards associated with penicillin cross-contamination prompted these agencies to initiate work to develop appropriate analytical methods for detection and quantitation of penicillin traces as a contaminant in non-antibiotic drug products (USFDA, 2015c).

However, based on the USFDA's experiences, through its regulatory activities, the problem has been shown unquestionably exist for many years and still exists today. In the inspection carried out to the pharmaceutical plant of SmithKline Beecham Limited ,GSK House, UK, It was documented in the warning letters findings of penicillin in non-penicillin manufacturing areas approximately 69 times in 2012, 72 times in 2013, 30 times in 2014, and 16 times through July 2015 even till 2016 (USFDA, 2016b). This leads to corrective actions to withhold approval of any new applications or supplements listing the firm as an API drug manufacturer. The main reason as reported was inadequate control to prevent cross-contamination from an area dedicated to penicillin manufacturing to other manufacturing areas and limitations of the current analytical test methods to detect the penicillin as a contaminant to the safe level.

1.3 Hypothesis

It was hypothesized that the idexx SNAP® biosensor kit and UPLC are two analytical techniques that can be used for detection of penicillin as contaminants in non-penicillin drugs. The Idexx SNAP® biosensor kit that was used for detection of β-lactam residues in milk samples can be utilized as a fast qualitative screening tool to evaluate amoxicillin cross-contamination to ibuprofen tablets 400 mg in the pharmaceutical industry. The detection limit of the method can reach the established safe level of amoxicillin (10 ppb) established by the USFDA regulatory guidelines. The UPLC method can be used for quantitative determination of amoxicillin traces in ibuprofen tablets 400mg, with detection limit that meet the regulatory requirements .

1.4 Objectives

1.4.1 General Objective

The overall objective of this research project was to develop and validate reliable analytical methods to detect penicillin cross-contamination in non-penicillin drug products.

1.4.2 Specific Objectives

a) To develop a quantitative analytical method for the determination of trace amounts of amoxicillin as penicillin contaminant in ibuprofen tablets 400mg using an UPLC system.
b) To validate the UPLC method using the ICH guidelines Q2 (R1).
c) To use the idexx SNAP® Biosensors kits for the development of a fast and simple screening method to detect the amoxicillin in drug products of ibuprofen tablets 400 mg.
d) To validate the SNAP® kit test method according to the decision of the European Commission (2002/657/EC).concerning the performance of analytical methods and interpretation of results.

1.5 Significance of the Study

A thorough literature review revealed only two methods for the detection of penicillin residues in non-penicillin drugs. The first microbiological procedure reported by USFDA in 1977 had the drawbacks of being time-consuming and was limited to the detection of penicillin G and ampicillin without including other β-lactam antibiotics (Carter, 1977). The other method used HPLC coupled with mass spectrometry but was restricted to the detection of penicillin (amoxicillin, ampicillin, and flucloxacillin) in funguard lyophilized drug product and detection limit of 30 ppb which is higher than the safe level (Akada *et al*., 2005).

This study is considered essential as it gives valuable information for determination of penicillin traces in non-penicillin drug products. Amoxicillin as a penicillin contaminant was capable of being detected at the safe level (10ppb) in the non-penicillin drug product. The study was done using two of the new techniques in pharmaceutical analysis. The first technique was UPLC which is considered an improved class of the traditional HPLC system. The advantages of UPLC over the HPLC was reported to be short turnaround time, method reliability, method sensitivity, and specificity (Gumustas *et al.*, 2013). The second method was the idexx SNAP® biosensor kit which is one of the rapid test kits approved by the USFDA for detection of β-lactam antibiotics in milk samples. However, it has not been used untill this point in pharmaceutical applications. The benefits of using the Idexx SNAP® include easy of handling, rapidity of testing and design for single use application so there is no chance for contamination or carry-over from previously tested samples. The total assay time for determination of amoxicillin in ibuprofen tablets using the Idexx SNAP® is 10 min. Applying these approaches will potentially reduce the time required to release the tested products to the market and ensure the safety of the patient.

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