DEVELOPMENT AND CHARACTERISATION OF PARACETAMOL HONEY SUSPENSION

BY

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ABSTRACT

Paracetamol (PCM) is a common analgesic and antipyretic drug used worldwide which is available in various dosage forms such as tablet, capsule, suppository, syrup and suspension. PCM suspension available in the market contains high amount of sugar to mask the bitter taste of PCM. High sucrose content will lead to health problems such as dental caries especially in children who frequently have fever and colds. This study aimed to explore the potential of honey to substitute sugar in PCM suspension. Honey is widely known as a natural sweetener. Besides, it contains micronutrients such as vitamins and enzymes that give a wholesome benefit such as antibacterial and antifungal properties. Compatibility study was performed on the API and its binary mixture with excipient using differential scanning calorimetry (DSC) and supported by attenuated total reflectance (ATR). DSC results showed incompatibility between PCM and parabens where the melting peak of PCM disappeared. However, ATR spectra of those combinations excluded these incompatibilities. Preliminary lab scale of paracetamol honey suspension (PHS) for 2 L was done with the incorporation of colloid mill for 10 minutes. The lab scale PHS had 689.2 ± 50.8 nm particle size, 0.518 ± 0.051 span, -47.76 ± 1.20 mV zeta potential, 5.36 ± 0.04 pH and 692.6 ± 7.5 mPa.s viscosity. These characteristics were similar to the Panadol® suspension. Analgesic and antipyretic activities of the suspension compared against Panadol® were also performed on Sprague-Dawley rats using hot plate method and Brewer's yeast-induced pyrexia model respectively. PHS had prolonged analgesic activity up to 180 minutes compared to Panadol® suspension which was 120 minutes. PHS had similar antipyretic activity with Panadol® suspension. Analytical methods verification (AMV) of PHS including specificity, peak purity, linearity, limit of detection (LOD), limit of quantification (LOQ) and intermediate precision was performed using HPLC. Besides, AMV of 4-aminophenol including specificity, peak purity, LOD and LOQ was also performed. All the AMV parameters met all the compendial specifications. PHS was scaled-up to 500 liters to identify optimum processing parameters such as mixing time, mixing speed, milling gap size and milling time. Based on scale-up results, milling gap size and time significantly ($p<0.05$) reduce particle size, polydispersity index (PdI), zeta potential and viscosity of the suspension. Samples from scale-up process were taken and stored in both real time and accelerated stability chambers for stability study. All stability study characteristics including appearance, assay, 4-aminophenol content, pH, total aerobic microbial count (TAMC), total yeasts and moulds count (TYMC), absence of *E. coli* at all-time points met all the compendial specifications except for appearance of the suspension at 6-month accelerated stability point which was more brownish due to honey that underwent Maillard reaction. Once the optimum processing parameters were identified, process validation (PV) was conducted and subjected to the same characterisations as the scale-up PHS. The PHS was successfully manufactured for commercialisation. In conclusion, the PHS was successfully manufactured for this pre-commercialisation stage. The suspension met all the compendial specification and is regarded as safe, effective and of good quality.

خلاصة البحث

الباراسيتامول (PCM) هي أدوية مسكنة للألم وخافضة للحرارة وتستخدم في جميع أنحاء العالم وهي متوفرة في أشكال جرعية مختلفة مثل الأقراص، والمستعلقات. يحتوي مستعلق الباراسيتامول على كمية عالية من السكر لإخفاء الطعم المر للباراسيتامول. مستوى السكروز العالي يؤدي تسوس الأسنان، وخاصة في الأطفال الذين يعانون من الحمى ونزلات البرد بشكل متكرر. تهدف هذه الدراسة إلى استكشاف إمكانية العسل لاستبدال السكر. يعرف العسل كمُحلٍ طبيعي، بالإضافة إلى احتوائه على مغذيات دقيقة مثل الفيتامينات والانزيمات المتميزة كمضاد للجراثيم والفطريات. أجريت دراسة التوافق على المكونات الصيدلانية الفعالة (API) وعلى جميع الخلطات الثنائية بالسواغات باستخدام قياس السعرات التفاضلي (DSC) وبالانعكاس الكلي المضعف (ATR). أظهرت نتائج الـ DSC عدم التوافق بين الباراسيتامول والبارابين حيث اختفت ذروة الباراسيتامول. ولذلك استبعدت أطياف الـ API لهذا الخليط حالات عدم التوافق هذه. تم صنع المستعلق الأولي للعسل والباراسيتامول بكمية 2 لتر بالخلط في مطحنة غروانية. كان لدى مستعلق العسل والباراسيتامول بالكمية المخبرية الخواص الآتية، حجمالجسيمات:689.2±50.8نانومتر،الامتداد:0.518±0.051،جهدزيتا:-47.76±1.20 ملفولت، ودرجة حموضة: 5.36 ± 0.04، ولزوجة: 692.6 ± 7.5 ميلي باسكال في الثانية. تم تنفيذ اختبار أنشطة تسكين الألم باستخدام طريقة اللوح الساخن وخفض الحرارة باستخدام نموذج بيركسيا لبريور المحرض بالخميرة للمستعلقة ومقارنةً بمستعلق البانادول على فئران. كان لدى المستعلق فترة نشاط طويلة لتسكين الألم مقارنة بمستعلق البانادول. كان النشاط الخافض للحرارة للمستعلق مماثلا لمستعلق البانادول. تم التحقق من الأساليب التحليلية (AMV) لمستعلق العسل والباراسيتامول بما في ذلك النوعية باستخدام الاستشراب السائلي العالي الأداء (HPLC). لبت مؤشرات الـ AMV جميع المواصفات المختصرة. وعلاوة على ذلك، تم توسيع نطاق مستعلق العسل والباراسيتامول حتى 500 لتر لتحديد مؤشرات التصنيع المثلى، مثل وقت الخلط، وسرعة الخلط، وحجم فجوة الطحن، ووقت الطحن. بالإضافة إلى ذلك، تم أخذ عينات من عملية توسيع النطاق وتخزينها في غرف الاستقرار ذي الوقت الحقيقي والمسرَّعة لدراسة الاستقرار. لبت جميع خصائص دراسة الاستقرار المواصفات المختصرة، وكان ذلك في جميع النقاط الزمنية، باستثناء مؤشر المظهر بعد 6 أشهر في نقطة الاستقرار المسرَّعة. تم اتباع المواصفات توسيع النطاق للمستعلق في التحقق من صحة العملية. لبى المستعلق جميع المواصفات المختصرة وهو آمن وفعال وذي نوعية جيدة.

APPROVAL PAGE

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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 ABBREVIATION

API	Active Pharmaceutical Ingredient
ACC	Accelerated
ATR-FTIR	Attenuated Total Reflectance Fourier-Transform Infrared Spectroscopy
BP	British Pharmacopoeia
CPP	Critical Process Parameters
CQA	Critical Quality Attributes
DSC	Differential Scanning Calorimetry
DPMO	Defects per Million Opportunities
HPLC	High Performance Liquid Chromatography
HSM	Hot Stage Microscope
IPQC	In Process Quality Control
LSL	Lower Specification Limit
NPRA	National Pharmaceutical Regulatory Agency
PCM	Paracetamol
PdI	Polydispersity Index
PHS	Paracetamol Honey Suspension
PV	Process Validation
QTPP	Quality Target Product Profile
RH	Relative Humidity
RT	Real Time
SEM	Scanning Electron Microscope
SC	Sodium Citrate
SMP	Sodium Methyl Paraben
SPP	Sodium Propyl Paraben
TAMC	Total Aerobic Microbial Count
TYMC	Total Yeast and Mould Count
USL	Upper Specification Limit
USP	United States Pharmacopoeia
XG	Xanthan Gum

CHAPTER ONE

INTRODUCTION

1.1 BACKGROUND OF THE STUDY

Paracetamol or acetaminophen, developed by Von Mehring in 1893, is a weak acidic drug with poor water solubility. Paracetamol is the first line analgesic agent and top selling over the counter antipyretic. Paracetamol prescribed for mild and moderate pain also contributes over USD 1 billion sales annually (Brune, Renner, & Tiegs, 2015).

Liquid form medication is intended for administration in children or adults, especially elderly that may have difficulty in swallowing solid dosage in tablet or capsule form. At lower concentration, for example 120 mg/5 mL strength of dose, PCM can be formulated into syrup formulation (a single phase solution). However, the syrup dosage form needs higher volume to be administered for greater dose, prompting the development of PCM suspension. The suspension is a multiple phase system consisting of well dispersed solid particles (PCM or active pharmaceutical ingredients) suspended in liquid phase that consists of variety of agents (suspending agent, flocculating and deflocculating agents, surfactants and agent that can reduce sedimentation rate). The existing formulation employs 12 or more excipients (Subramaniam & Nandan, 2012; Tangri, Madhav, & Khurana, 2011).

On top of that, the quantity of sugar such as sucrose, glucose and sorbitol used is extremely high ranging from 11 - 66% of the total volume (Babu, Doddamani, Naik, & Jagadeesh, 2014; Lustig, Schmidt, & Brindis, 2012; Subramaniam & Nandan, 2012). High sugar content in paediatric liquid medications concerns many researchers on the development of dental caries (Maguire, Rugg-Gunn, & Butler, 1996; Mariotti

& Lucisano, 2014; Subramaniam & Nandan, 2012) in children especially in those with long term medication and who take medication frequently due to coughs and common colds.

Honey is a sweet, highly viscous fluid produced by honey bees from nectar derived from flowers. It contains a complex mixture of carbohydrates, mainly fructose and glucose while other sugars are present as traces. Honey also contains a variety of minerals and microelements, in which the types are depending on the floral origin (Adams, Manley-Harris, & Molan, 2009; Vallianou, Gounari, Skourtis, Panagos, 2014).

Therefore, honey was employed not only for its favourable Newtonian fluid (Cohen & Weihs, 2010; Witczak, Juszczak, & Gałkowska, 2011) properties but also for its wholesome benefits including as sweetener, flavouring agent, thickener and suspending agent (Robert & Ismail, 2009). A study conducted by Erejuwa, Sulaiman, & Ab Wahab (2012) reported that administration of honey orally or via inhalation was reported to reduce considerably the concentrations of blood glucose in patients with type 2 diabetes mellitus. In type 1 diabetic patients, honey was shown to produce lower blood glucose compared to sucrose and glucose, indicating its lower glycaemic index (Chepulis & Francis, 2013; Deibert, König, Kloock, Groenefeld, & Berg, 2010).

In addition, consumption of PCM in early stage of infant and childhood was reported to be associated with increased incidence of asthma and allergic later in their life (Henderson & Shaheen, 2013). On the other hand, many studies by Al Ameen et al. (2011), El-Aidy et al. (2015) and Kamaruzaman, Sulaiman, Kaur, & Yahaya (2014) have reported that honey to be a promising alternative treatment for asthma by reducing airway inflammation.