FORMULATION AND EVALUATION OF PEDIATRIC CARBAMAZEPINE SUSTAINED RELEASE ORAL JELLY

BY

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ABSTRACT

Once daily epilepsy carbamazepine (CBZ) medication oral jelly for pediatrics was prepared and evaluated. The available marketed CBZ pediatric dosage form is CBZ suspension only which is not sustained release medication. Therefore, developing new CBZ sustained release oral jelly can play an important role to handle the following issues; (1) suitable dosage form for easy swallowing (2) reducing the multiple daily doses to one daily dose for patient convenience. This work consists of three parts, first one is to prepare CBZ sustained release microparticles, the second part is to incorporate the microparticles in alginate beads and the final one is to suspend the beads in oral jelly. The microparticles prepared by solvent evaporation method utilizing EC as sustained release polymer. Microparticles were evaluated for particle size, encapsulation efficiency (EE), *in vitro* release test, differential scanning calorimetry (DSC), attenuated total reflection–fourier transform infrared spectroscopy (ATR-FTIR), and high-pressure liquid chromatography (HPLC). CBZ release from microparticles was achieved and compared to the release of CBZ sustained release tablets of 200 mg stated in United States Pharmacopoeia (USP). The beads fabricated by crosslinking of sodium alginate with calcium chloride solution utilizing electrospray. CBZ beads were tested for the size, morphology, in vitro drug release and HPLC. *In vitro* release study results of CBZ from the beads showed the same release of CBZ in microparticles. Finally, the CBZ oral jelly prepared using an iota carrageenan gelling agent and evaluated for the dissolution test, syneresis, rheology, drug content uniformity, viscosity, physical appearance, and stability. CBZ loaded microparticle size ranged from 131 to 186 μm. The highest EE was 96% for MP2 and the lowest one was 74% for MP9. The cumulative release percentage of CBZ at 24 h was ranged from 49% in MP1and 89% in MP10. CBZ bead results showed bead size of 1.4 mm for B2 and 3.5 mm for B4 with same EE of CBZ loaded microparticles. The release of CBZ from its beads was almost equal for all prepared bead formulations. *In vitro* drug release of CBZ was done firstly in the same conditions of dissolution test of CBZ beads and CBZ microparticles to ensure that there was no change in the release of CBZ when fabricated in iota carrageenan jelly. Secondly, comparison dissolution test study was carried out between CBZ oral jelly and Tegretol® XR 200 mg tablets and similarity factor was calculated to ensure that the CBZ jelly matching to the guidelines. Stable and homogenize CBZ oral jelly was obtained with the release similarity factor (F2) of 76 between CBZ oral jelly and Tegretol® XR 200 mg tablets under the same release conditions. The release of CBZ from the jelly found to be 94.11% from the original concentration after 24 hours. This study developed a new CBZ dosage form for pediatric patients with sustained release property and could be used as main and alternative treatment for pediatric epilepsy patients.

خلاصة البحث

بسبب عدم توفر دواء الكاربامازبين ذو الامتصاص البطيء للاطفال تم تحضير وفحص كاربامازبين الاطفال ذو الامتصاص البطيء الذي يمكن ان يلعب دورا هاما في علاج الكثير من المشاكل , ابرزها (1) شكل علاجي جديد يسهل من عملية البلع (2) تقليل عدد الجرع اليومية لدواء الكاربامازبين الاعتيادي من عدة جرع الى جرعة واحدة حيث يسهل استخدام الدواء سواء للمريض او المرافقين له. هذا المشروع او البحث يتكون من ثلاثة اجزاء رئيسية وهي: الجزء الاول متضمنا تحضير الكاربامازبين على شكل حبيبات مجهرية صغيرة تتضمن تحرير الدواء ببطيء. الجزء الثاني هو تغليف حبيبات الكاربامزبين المجهرية الصغيرة في كرات الجينات الصوديوم والجزء الاخير هو لتعليق كرات الجينات الصوديوم في هلام الكاراجينان. تحضير الجزء الاول وهو حبيبات الكاربامازبين المجهرية الصغيرة كان باستخدام طريقة تبخير المذيب باستخدام الايثايل سليلوز كبوليمر يساعد على عملية تحرير الدواء ببطيء. تقييم وفحص حبيبات الكاربامازبين الصغيرة كان باستخدام فحص تحرير الدواء, فحص كفاءة التغليف, فحص حجم الحبيبات, فحص شكل الحبيبات, المسح الحراري التفاضلي , الضغط العالي لفصل السوائل, وفحص طيف الاشعة تحت الحمراء. اظهرت نتائج فحص الحبيبات المجهرية لدواء الكاربامازبين تطابقا جيدا مع فحص تحرير الدواء من اقراص الكاربامازبين 200 ملغم المنصوص عليها في دستور الادوية الامريكي تحت نفس الظروف. تحضير كرات الجينات الصوديوم كان باستخدام تقنية التوزيع الكهربائي لالجنيت الصوديوم في محلول الكالسيوم كلورايد عن طريق تكوين كرات صلبة بفضل تشعب محلول الكالسيوم كلورايد مع الصوديوك الجنبيت المخلوط مع حبيبات الكاربامازبين المجهرية الصغيرة. كرات الجنبيت الصوديوم المتكونة كانت قد فحصت لشكلها الخارجي, حجمها, فحص تحرير الكاربامازبين من هذه الكرات اولا ثم من حبيبات الايثايل سليلوز ثانيا, فحص الضغط العالي لفصل السوائل. نتائج فحص تحرير الكاربامازبين من كرات الالجنبيت كانت مطابقة للخطوة السابقة من التحضير مما يدل على ان الخطوة الثانية لم تغير تحرير الكاربامازبين اثناء تغليفه بكرات الجنبيت الصوديوم. الخطوة الاخيرة من هذا المشروع تضمن تعليق كرات الصوديوم الجنيت داخل هلام الايوتا كاراجينان حيث تم تقييم هلام الايوتا كاراجينان اولا بفحص الخواص الجريانية لهذا الهلام, فحص فصل الماء عن الهلام اثناء الخزن, فحص المظهر الخارجي للهلام, فحص لزوجة الهلام , فحص تحرير الكاربامازبين من الهلام واخيرا اختبار الضغط العالي لفصل السوائل.

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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TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATION

CBZ	Carbamazepine
EC	Ethylcellulose
MR	Modified release
EA	Ethyl acetate
PVA	Polyvinyl alcohol
EE	Encapsulation efficiency
DT	Dissolution test
PS	Particle size
EMA	European medicines agency
CHMP	Committee for medicinal products for human use
MR	Modified release
DSC	Differential scanning calorimetry
HPLC	High-pressure liquid chromatography
FTIR	Fourier transform infrared spectroscopy
MP	Microparticles
B	Beads
J	jelly
BBB	Blood-brain barrier
WHO	World health organization
HPMC	Hydroxypropylmethylcellulose
SF	Sphericity Factor
F2	Similarity Factor
HCl	Hydrochloric acid
GIT	Gastro-intestinal tract
FDA	Food and drug administrative
USP	United states pharmacopoeia

LIST OF SYMBOLS

®	Trade name
°	degree
p	P value
µ	micro
Σ	Sigma

CHAPTER ONE

INTRODUCTION

1.1 BACKGROUND

Pharmaceutical dosage forms for pediatrics must be appropriate in relation to their age. Pediatrics below 6 years generally cannot have solid dosage forms by oral route unlike liquid and semi-solid dosage forms. According to European Medicines Agency (EMA) Committee for Medicinal Products for Human Use (CHMP), there is a number of important considerations to be noted when manufacturing a new dosage form for pediatrics and as following (Committee, 2006):

1. Minimizing the frequency of dosage.
2. Minimizing non-toxic excipients.
3. Reliable, easy, convenient administration.
4. Should be inexpensive and available commercially.
5. Should be easily prepared, elegant and stable.
6. One dosage form suits all or a full of a range of pediatrics.

EMA (CHMP) mentioned that modified release (MR) preparations can be helpful for child patients who may need to have medication when they are at school or in the night. In oral modified release medications, single dose daily formulations can be advantageous for compliance. While MR injections can minimize significantly the frequency of the dose but the pain must be avoided. Transdermal formulations can also prolong the effect of the drug with simple use but the skin permeability level will be different with age developmental changes and this issue must be taken in the consideration when preparing such a dosage form. MR formulations should meet the

requirements of the dose for a different range of ages.In the MR solid preparations, the dosage requirements can be achieved by using specified formulations like prolonged release granules with known dose per granule. Liquid MR dosage forms ingredients are dissolved in or be bound to very small particles like pellets or resin particles. MR oral suspensions contain pellets or small particles and size of that particles and pellets is limited and child patient must not chew it(Committee, 2006).

Epilepsy is one of a brain function disorders characterized mostly by frequent and unpredictable obstruction of the function of the normal brain, known as epileptic seizures. It's the abnormality of a sudden electrical activity (Fisher et al., 2005). This disorder is affecting about 70,000,000 worldwide of different ages in 2014 (Ali & Nabi, 2014). Different reasons were reported to know the causes behind epilepsy syndrome such as the zone of the brain involved, genetic reasons, age etc. (Berg, Levy, Testa, & Shinnar, 1999). There are many types of epilepsy syndrome like; Juvenile absence epilepsy, Angelman syndrome, childhood absence epilepsy, Doose syndrome, Dravet syndrome, epilepsy on infancy with migrating focal seizures, epilepsy with myoclonic absence, frontal lobe epilepsy, epilepsy with generalized tonic-clonic seizers alone, hypothalamic hamartoma, *lafora* progressive myoclonus epilepsy, PCDH19 epilepsy, and reflex epilepsy etc.(Kramer et al., 1998; U. Lee, Kim, & Jung, 2006).

CBZ is an anticonvulsant drug used to treat focal seizures, trigeminal, neuralgia, and bipolar disorder. The site of absorption of CBZ is the gastrointestinal tract (GIT) but it has faster absorption on a full stomach than an empty stomach. CBZ is a white or white-yellowish particles, bitter in taste, insoluble in water. CBZ shows its anticonvulsant or antiepileptic effect by inhibiting voltage-dependent sodium channel, thus it blocks sustained repetitive firing in individual neurons. It seems to

give no help in GABA-mediated inhibition (Catterall, 2014). Diplopia, headache, dizziness, nausea and vomiting are the common side effects of CBZ while the rare side effects of CBZ includes erythema multiform, Stevens-Johnson syndrome, Reversible mild leucopenia, blood dyscrasias and toxic hepatitis (Perucca & Gilliam, 2012).

Jellies can be defined as "a semisolid system consisting of either suspension made up of gelling agent molecules interpenetrated by a liquid" (Jones, Swarbrick, & Boylan, 2002). Medicated jellies more reasonable for pediatric, many studies have suggested that the using of oral semi-solid dosage forms are preferred for dysphagic, children and geriatric patients because of their formulation's nature as semi-solid preparations (Yutaka Inoue & Kanamotoa, 2015). Oral jelly is a fundamental solution to dysphagia patients, and also is frequently prescribed for geriatrics (Prakash et al., 2014).

1.2 PROBLEM STATEMENT

Despite the availability of sustained release formulations of carbamazepine, these formulations are not designed for pediatric patients. Pediatric patients with epilepsy need to take carbamazepine suspension divided into two or four times a day for long duration (Wolters Kluwer Health, 2017). There are no available marketed sustained release dosage forms to be used for pediatrics. The available dosage form is only (carbamazepine suspension) giving no options for those patients or their caregivers. Providing sustained release formulation of CBZ may help pediatrics in administering the drug with more convenience. The new sustained release dosage form should be flexible in dosing (mg drug per body weight) and suitable for pediatrics of different ages. For these reasons, chewable tablets and dispersible tablets may not achieve the

desired criteria. Instead, oral jellies that appeared as new dosage form might be a potential candidate.

1.3 HYPOTHESIS

CBZ can be prepared for pediatric-suitable sustained release jelly formulation. The formulated oral jelly has similar release profile as the reference.

1.4 OBJECTIVE

General objective:

To formulate CBZ in sustained release oral jelly formulation, suitable for pediatric use.

Specific objectives:

1. To fabricate sustained release CBZ microparticles by a solvent evaporation method using ethylcellulose polymer.
2. To characterize CBZ loaded microparticles for their particle size, encapsulating efficiency, *in vitro* drug release, morphology study, HPLC, ATR-FTIR, and DSC.
3. To load CBZ microparticles in alginate beads and characterize it for beads size, morphology study, encapsulation efficiency, *in vitro* drug release, and HPLC.
4. To suspend the beads in the jelly vehicle and characterize it for the syneresis, rheology, homogeneity test, *in vitro* drug release, and stability study.

1.5 STUDY DESIGN

This project is divided into three main parts: first, is the fabrication of CBZ-loaded microparticles using EC as encapsulating polymer. These microparticles are optimized

to have sustained release profile similar to the commercially approved sustained release CBZ tablets. Since microparticle may have grittiness feeling in the mouth when taken orally, they were entrapped in alginate beads. Alginate beads have better mouth feeling, jelly texture and biocompatible. Hence, the second part is the preparation of alginate beads containing CBZ microparticles. The beads are designed so that they have minimal effect on the release profile of the microparticles. Finally, is the preparation of jelly base to suspend alginate beads. The jelly acts as a vehicle to suspend the beads, preventing them from settling down and giving pediatric-friendly texture to be administered. Similarly, the jelly was optimized to have minimal effect on the release of CBZ from the microparticle. Therefore, the final dosage form will have same release profile of the microparticles, which is like the commercially available CBZ tablets.

CHAPTER TWO

LITERATURE REVIEW

2.1 INTRODUCTION

Developing a new dosage form is a real challenge to the pharmaceutical researchers, especially when the dosage form targets pediatric population. Pediatrics differ from adults in the type of dosage forms and the doses of the medications which considered to be constant in the adults and depended on the body weight for pediatrics. There are a differences in the pharmacodynamic and pharmacokinetic properties as the pediatrics have grown and organ developing stage (Estabrook, Bouxsein, Pitluck, & Davis, 2000).

There are different age groups named according to pediatrics developmental stages of their population (Committee, 2006) like:

- Pre- newborn infants.
- Newborn infants aged (from 0 to 27) days.
- Infants and toddlers aged (1-23) months.
- Children aged (from 2 to 11) years.
- Adolescents aged (12-16 or 18) years.

2.2 PHARMACOLOGICAL DEVELOPMENT OF PEDIATRIC POPULATION

Children are growing and many physiological and pharmacological changes occurred during their life. Understanding those changes can give an idea to handle and manufacture the suitable medications. A brief summary is explained for absorption,

distribution, metabolism and renal elimination in pediatrics to understand the best way of bioavailability of any medication prescribed for their use and as follows (Committee, 2006):

2.2.1 Absorption

The different site of drug absorption of children can be explained by the following discussion:

2.2.1.1 Oral

In the neonatal stage, gastric pH is high with increasing of gastric emptying, therefore the rate of absorption for drugs administered orally is faster in older pediatrics than neonates and infants (Heimann, 1980).

2.2.1.2 Buccal

The permeability of mucosa considered to be higher in pediatrics than adults (Committee, 2006).

2.2.1.3 Topical

Pediatrics have large surface area compared to adults, therefore percutaneous absorption is more. Topical substances have potential absorption through the skin of pediatrics o reach blood circulation and body tissues and may cause toxicity (for example, adrenal suppression with topical corticosteroids). Epidermis layer in childhood is more perfused and hydrated than adults and stratum corneum is thinner (Committee, 2006; Monsour, Rabinovitch, & Dean, 1999).

2.2.1.4 Intramuscular

Due to the rich supply of blood capillaries in infants than older pediatrics and adults, the absorption will be greater in infants (Simons, Roberts, Gu, & Simons, 1998).

2.2.1.5 Pulmonary

Absorption through lungs mucosa can be useful but drugs administered locally are well absorbed in pediatrics but may produce systemic side effects (Committee, 2006).

2.2.1.6 Rectal

Suppositories can be used for infants and can give good absorption but they will be an issue for older pediatrics (Maeda, Nakano, Aoyama, Matsumoto, & Fujito, 2016).

2.2.1.7 Nasal

Intranasal is a useful route of administration for pediatrics and can be considered as good absorption route and more preferred for pediatrics than injection but irritation or "a runny nose" and pain may be produced by formulations. Nasal mucosa secretion can also influence the absorption (Maggio, 2016).

2.2.1.8 Distribution

Age-related changes can be found in body composition especially protein binding and the transport mechanism. In infancy blood-brain barrier (BBB) is considered as immature part of their body (Allegaert, Velde, & Anker, 2014).