การพัฒนาสูตรตำรับยาเม็ดออกฤทธิ์นานแบบหลายชั้นของตัวยาผสมโซเดียมวาลโปรเอทและกรดวาลโปรอิก

นางสาววรวรรณ สายงาม

วิทยานิพนธ์นี้เป็นส่วนหนึ่งของการศึกษาตามหลักสูตรปริญญาเภสัชศาสตรมหาบัณฑิต
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FORMULATION DEVELOPMENT OF MULTILAYER SUSTAINED RELEASE TABLETS OF SODIUM VALPROATE COMBINED WITH VALPROIC ACID

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A Thesis Submitted in Partial Fulfillment of the Requirements

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วรวรรณ สายงาม : การพัฒนาสูตรตำรับยาเม็ดออกฤทธิ์นานแบบหลายชั้นของตัวยาผสมโซเดียมวาลโปรเอทและกรดวาลโปรอิก (FORMULATION DEVELOPMENT OF MULTILAYER SUSTAINED RELEASE TABLETS OF SODIUM VALPROATE COMBINED WITH VALPROIC ACID) อาจารย์ที่ปรึกษาวิทยานิพนธ์ : รศ.ดร.พจน์ กุลวานิช, 123 หน้า.

วัตถุประสงค์ของการศึกษา คือ การกำหนดสูตรตำรับและการประเมินผลชนิดและปริมาณของพอลิเมอร์ต่ออัตราการปลดปล่อยตัวยาโซเดียมวาลโปรเอทออกจากยาเม็ดระบบเมทริกซ์ และการพัฒนาสูตรและวิธีการผลิตยาเม็ดออกฤทธิ์นานแบบหลายชั้นของตัวยาโซเดียมวาลโปรเอทเดี่ยว และตัวยาผสมโซเดียมวาลโปรเอทและกรดวาลโปรอิก เตรียมโดยวิธีตอกตรง ใช้คอลลอยดอล ซิลิกอน ไดออกไซด์ ทำหน้าที่เป็นสารช่วยดูดซับ (ปรับเปลี่ยนปริมาณในช่วงร้อยละ 2.5-5 โดยน้ำหนัก) ใช้ทัลคัมและไดเบสิคแคลเซียมฟอสเฟตเป็นสารประกอบในตำรับ ส่วนชนิดของพอลิเมอร์ที่นำมาศึกษา ได้แก่ เอทิลเซลลูโลส, ไฮดรอกซีโพรพิลเมทิลเซลลูโลส (HPMC E4M, K15M), แซนแทนกัม, คาราจีแนน, โซเดียมแอลจิเนต, คอลลิดอนเอสอาร์ และยูดราจิทอาร์เอสพีโอ (ปรับเปลี่ยนปริมาณในช่วงร้อยละ 5-20 โดยน้ำหนัก) จากการศึกษาพบว่า ไฮดรอกซีโพรพิลเมทิลเซลลูโลส (HPMC K15M) มีคุณสมบัติในการควบคุมการปลดปล่อยตัวยาได้ดีกว่าพอลิเมอร์ชนิดอื่น ซึ่งปริมาณของไฮดรอกซีโพรพิลเมทิลเซลลูโลสมีผลต่อการปลดปล่อยตัวยาจากระบบ นอกจากนี้ยังนำไฮดรอกซีโพรพิลเมทิลเซลลูโลสมาใช้ควบคุมการปลดปล่อยตัวยาในชั้นประกบของยาเม็ดออกฤทธิ์นานแบบหลายชั้นด้วย พบว่าสูตรตำรับยาเม็ดออกฤทธิ์นานแบบหลายชั้น สามารถปลดปล่อยตัวยาได้นานถึง 24 ชั่วโมง โดยยาเม็ดออกฤทธิ์นานแบบหลายชั้นของตัวยาโซเดียมวาลโปรเอทปลดปล่อยตัวยาได้เร็วกว่าตัวยาผสมโซเดียมวาลโปรเอทและกรดวาลโปรอิก นอกจากนี้ยังพบว่าการปลดปล่อยยาเป็นไปตามสมการอันดับศูนย์ (zero order) และมีกลไกการปลดปล่อยยาโดยการแพร่แบบ non-fickian

ภาควิชาวิทยาการเภสัชกรรมและเภสัชอุตสาหกรรม ลายมือชื่อนิสิต.....

สาขาวิชาเภสัชอุตสาหกรรม ลายมือชื่อ อ.ที่ปรึกษาวิทยานิพนธ์หลัก.....

ปีการศึกษา 2555 ลายมือชื่อ อ.ที่ปรึกษาวิทยานิพนธ์ร่วม.....

5276589533 : MAJOR INDUSTRIAL PHARMACY
KEYWORDS : SODIUM VALPROATE / VALPROIC ACID / MATRIX TABLET / MULTILAYER TABLET / SUSTAINED RELEASE TABLET

WORAWAN SAINGAM : FORMULATION DEVELOPMENT OF MULTILAYER SUSTAINED RELEASE TABLETS OF SODIUM VALPROATE COMBINED WITH VALPROIC ACID. ADVISOR : ASSOC. PROF. POJ KULVANICH, Ph.D., 123 pp.

The purpose of this study was to formulate and evaluate the effect of different polymers on drug release from sodium valproate matrix tablet and develop multilayer sustained release tablets that composed of sodium valproate only and combined with valproic acid. They were prepared by direct compression method using various amount of colloidal silicon dioxide (2.5-5%w/w) as an adsorbent, talcum, dibasic calcium phosphate as excipients. The polymers used were:, ethylcellulose, HPMC E4M, HPMC K15M, xanthan gum, carrageenan, sodium alginate, Kollidon® SR and Eudragit® RSPO (5-20%w/w). Among the eight polymers, HPMC K15M led to more retardation of drug release. The concentration of HPMC K15M employed in tablet formulations affected drug release from matrix tablets. Then, HPMC K15M was also used as a rate controlling polymer in the outer layers. The drug released from multilayer formulations were sustained for 24 hours. The formulation that composed of only sodium valproate released drug from tablet faster than that composed of sodium valproate combined with valproic acid. Drug release profiles of multilayer sustained release tablets of sodium valproate and those of sodium valproate combined with valproic acid best fit to zero order release model, while the mechanism of drug release was non-fickian diffusion.

Department: Pharmaceutics and Industrial Pharmacy Student's Signature……....
Field of Study: Industrial Pharmacy Advisor's Signature……....
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CONTENTS

Page

Page

LIST OF TABLES

LIST OF FIGURES

Figure Page

Figure Page

LIST OF ABBREVIATIONS

%	percentage
°C	degree Celsius (centrigrade)
HPMC	hydroxypropyl methylcellulose
DI	deionized
et al.	et alli, and others
mg	milligram (s)
g	gram (s)
HCl	hydrochloric acid
PBS	phosphate buffer solution
N	normality
min	minute (s)
ml	milliliter (s)
mm	millimeter (s)
pH	the negative logarithm of hydrogen ion concentration
R^2	coefficient of determination
RSD	relative standard deviation
SD	standard deviation

CHAPTER I
INTRODUCTION

Sodium valproate and valproic acid are different forms of the identical drug. All the information refers to just sodium valproate (2-propylpentanoic acid sodium salt). It is a useful drug widely employed for treatment of epilepsy, prevention of ictus epilepticus, simple and complex absence seizures (Ukigaya et al., 1996; Lin et al., 2004) and mood disorder. The effective blood concentration of the drug generally ranges from 50 to 100 μg/ml. Sodium valproate has a short biological half-life (Schapel et al., 1980). It must be administered three times a day to maintain an effective blood concentration. Since such a short dose interval is troublesome for patients, there have been many attempts to develop long-acting, sustained release preparation of sodium valproate (Ukigaya et al., 1996).

Recently proposed techniques for preparing sustained-release tablets of sodium valproate include (a) mixing with valproic acid (Aubert et al., 1991) and (b) incorporation of the drug in a matrix containing a rate-controlling polymer (Shoaib et al.,2006; Shankar et al., 2010).

Sodium valproate and valproic acid were used in a combination because there are insignificant in the pharmacokinetics of the formulations and approachability in a commercial product (Lin et al., 2004). Sustained release formulation of sodium valproate combined with valproic acid reduces the fluctuation in plasma drug concentrations, therefore decreasing or preventing plasma peak-related adverse events, and gives extended release action enabling a once or twice daily administration with inherent benefits in terms of patient compliance (Doughty et al., 2003).

However, sodium valproate is highly hygroscopic. Its formulations often poses problem during production and storage. Its highly water soluble drug, a common problem observed with matrix systems containing highly water soluble drugs is an initial burst release of the drug. Then, owing to oily characteristic of valproic acid, solid

dosage form (e.g.tablet formulation) is difficult to prepare. Therefore, production of sodium valproate and valproic acid tablet was required appropriate excipient and in low humidity condition.

Sustained release formulations are effective to controlling optimal therapy with the narrow therapeutic drugs and/or eliminate rapidly. Sustained release delivery systems are designed to carry the plasma level of a drug instantly to therapeutic concentrations via indicates of an initial dose part and then sustained the plasma level for a certain predetermined time with the maintenance part (El-Sayed et al., 1995). Sustained release of drugs in gastro-intestinal tract, an oral administration is not affected by the absorption process. As a result, it is necessary for the development phase of oral sustained release dosage forms to use dissolution methods that allow pharmacokinetic monitoring of the dosage forms, especially, the prediction of the bioavailability and the absorption rate. Sustained release formulations lead to more important in therapeutics as show that reduced adverse effects, reduced dosing frequency, thus improved patient comfort and compliance (Nandita and Sudip, 2003). The principal goal of sustained release dosage forms is the development of drug therapeutics evaluated by the relationship between advantages and disadvantages of the use of sustained release systems.

One method of manufacturing sustained release dosage forms is by the incorporation of the drug in a matrix containing a rate-controlling polymer (Ayhan et al., 2005), such as water soluble polymer, cellulose derivative (e.g. hydroxypropyl methylcellulose, methylcellulose, hydroxypropylcellulose, carboxymethylcellulose, etc.), synthetic water soluble polymers (e.g. polyvinylpyrrolidone, cross-linked polyvinylpyrrolidone, polyethylene oxide, etc.), polysaccharides (e.g. pullulan, dextran, etc.), etc. and other excipient (U.S. Pat. No. 495497).

In order to achieve a sustained release formulation, a variety of dosage forms have been developed. Among them, since simple ingredient, cost and ease of manufacture, many studies have been performed on a multilayer oral dosage form.

A multilayer oral dosage form that provides controlled release of an active ingredient includes a core layer containing a pharmaceutical active ingredient and/or a nutritional active ingredient and at least one release-controlling layer laminate to each side of the core layer. The dosage form can be prepared using simple, inexpensive tablet compression techniques (Zerbe et al., 2007).

An oral multilayer sustained release tablet, especially, a multilayer tablet is composing of an inner immediate-release layer containing a pharmaceutical and/or nutritional active ingredient and two outer layers containing swelling polymers. On exposure to aqueous medium, the two outer layers swell to form gelled layers surrounding the lateral side of the inner layer rapidly, thereby control effectively the releases of drug from the inner immediate-release layer (Park et al., 2010).

Nowadays, sodium valproate and valproic acid commercial product are available in different dosage forms; tablet, enteric-coated tablet, delayed-release tablet, capsule (liquid-filled), sprinkle, solution, intravenous, suppositories. All dosage forms have a short biological half-life, its have been administered three or four times a day to maintain an effective blood concentration. Since such a short dose interval is troublesome for patients, sustained release formulations have been developed to enhance the pharmacokinetic profile. However, some case of sustained release formulations is still generally administered twice daily. And all of sustained release formulations on a commercial product are prepare by matrix system. Therefore, the researcher is interested in multilayer sustained release formulation of sodium valproate and valproic acid that provides a viable resolution for delivering active ingredients using a cost-effective technology.

The purposes of this study were to formulate and evaluate the effect of different polymers on drug release from matrix tablets containing either sodium valproate or sodium valproate combined with valproic acid.

The objectives of this study were :

1. To develop and formulate multilayer sustained release tablet of sodium valproate and sodium valproate combined with valproic acid
2. To investigate the effect of types and amounts of polymer on sodium valproate release from matrix and multilayer sustained release tablet

CHAPTER II
LITERATURE REVIEW

Sodium valproate and valproic acid

Sodium valproate

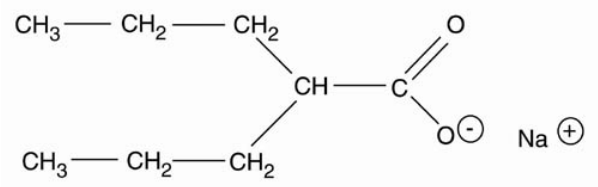


Figure 1 Structure formula of sodiumvalproate

Sodium valproate is a 2-propylpentanoic acid sodium salt. It is a salt of valproic acid indicated as sodium 2-propylpentanoate.

It has a molecular weight of 166.19. It occurs as an essentially white or almost white and odorless, crystalline, deliquescent powder, very hygroscopic powder and very soluble in water and slight to freely soluble in alcohol. Sodium valproate is very stable when dissolve in water, 0.1N sodium hydroxide and 0.1N hydrochloric acid. Then it is stable to sunlight in dry condition for 30 days.

Valproic acid

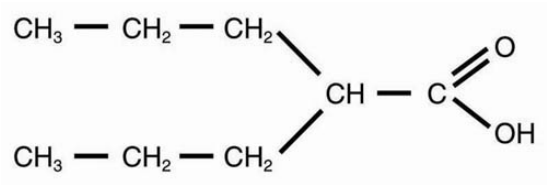


Figure 2 Structure formula of valproic acid

Valproic acid is a carboxylic acid indicated as 2-propylpentanoic acid. It is also recognize as dipropylacetic acid. Valproic acid (pKa 4.8) has a molecular weight of

144.21, boiling point is 219.5 °C. It occurs as a colorless liquid with a characteristic odor. It is slightly soluble in water (1.3 mg/mL). It is freely soluble in acetone, alcohol, chloroform, ether, benzene, *n*-heptane, methyl alcohol, 0.1N sodium hydroxide and slightly soluble in 0.1N hydrochloric acid. Valproic acid is very stable, no degradation by heat, light and strong acid or strong alkali.

Pharmacokinetics

Absorption and bioavailability

Valproic acid is rapidly absorbed oral administration is provided using regular formulations. It is found in serum, brain, cerebrospinal fluid (CSF), urine, saliva, breast milk, placenta and fetal tissue in significant levels. While on the contrary, it is almost completely bioavailable in human plasma. Hence, valproic acid has a high degree of ionization at pH 7.4, it is much less lipid soluble than other anticonvulsant (Loscher et al., 1984). Twenty percent of plasma drug is concentrated in the brain and CSF (Levy et al., 1995). Placenta transfer studies show that parent compound and some metabolites are present in cord blood in higher concentrations than in maternal blood (Nau et al., 1981). The levels of the drug in fetal circulation and placental tissue were found to be 28 ± 4 and 7 ± 3 % (Barzago et al., 1996, Fowler et al., 1989). Normally the levels of drugs in cord blood are equal or lower than that of maternal blood. Drug concentration in the breast milk was found to be only 3% of maternal plasma concentration (Nau et al., 1981). Valproic acid is strongly bound to serum albumin (>92%) (Fukuoka et al., 1998).

Metabolism

Valproic acid is predominantly cleared by biotransformation to give over 50 known metabolites that exert anticonvulsant activity (Levy et al., 1995). Even though valproic acid is a simple fatty acid, its metabolism is complex with variety of overlapping phase I and II pathways. It undergoes metabolism by a variety of oxidation and

conjugation processes, which result in formation of unsaturated compound 4-en-valproic acid and trans-isomer of 2-en-valproic acid were 60-100% as potent as the parent drug. Other metabolites are less lipid-soluble than parent compound; therefore, the brain concentrations of the metabolite are too low to produce any significant anticonvalsant acivity (Loscher et al., 1981). However, they involve in the side effect and toxicity of valproic acid including neurotoxic and hepatic side effect (Lavey et al., 1991, Bailly., 1992). In human, valproic acid is metabolized mainly by cytochrome P450 isoenzyme (Anari et al., 2000).

Excretion

The principal route excretion of the drug and its metabolites is the kindly with a half-life of 9-18 hours in human. In contrast to human, animal models have a lower elimination half-life ranging from 0.6-9 hours (Loscher., 1999). The elimination half-life of valproic acid and some metabolites was found to be much longer in the neonates (40-50 hours) than adult subjects (9-18 hours) (Loscher., 1999, Nau et al., 1981). One study reported no difference between the elimination half-life between elderly and young subjects (15.4 and 13.0 hours, respectively) while other found an increase in for older patients (14.9 versus 7.2 hours for young patients) (Loscher., 1999, Stephen., 2003). Insignificant amounts of valproic acid are found in breast milk, approximately 3% of maternal drug level (Nau et al., 1981).

Distribution and protein binding

The drug is highly bound to albumin (approximately 90%) (Hardman et al., 1996). Protein binding is concentration dependent and decrease at high valproate concentration (Hardman et al., 1996). Free fraction plasma protein concentration increase from approximately 10% at 40% µg/mL to 18.5% at 130 µg/mL (Hardman et al., 1996). Protein binding decrease particularly in elderly (Klotz et al., 1978), in patients with renal failure (Klotz et al., 1978), and liver disease (Lapierry et al., 1999)

Although sodium valproate and valproic acid have been shown to be effective in both as an epilepsy, an ictus epilepticus, a simple and complex absence seizures and mood disorder as it does several things in the brain. Firstly, gamma-aminobutyric acid (GABA) is inhibitor in the brain by other chemicals which break GABA down in the short period. In case of people with normal levels of GABA, prevents increasing of GABA. While, in some case it is not sufficient levels of GABA in the brain. Deficiency of GABA seems to stimulate to over-activity. Sodium valproate assists to breakdown of GABA and maintains the chemical in the brain to normal levels. Secondary, it may inhibit repetitive rousing of neurones. While a message is passed, there is a short refractory period before the next message can be passed, during which time the nerve ending resets itself. Sodium valproate may increase a refractory period by a few amount. At the normal condition, it is not different, but if the brain is overactive and lots of messages are being passed in quick succession, the effect of the sodium valproate will be to slow the number of messages back to the normal level. In case of anti-migraine action, valproic acid increase brain GABA level and in doing so may activate the GABA receptor and suppresses migraine-related events. (U.S. Pat. No. 20050276850)

Sustained release formulations

Oral sustained release formulations are developed to control the release of active ingredients (pharmaceutical or nutritional) at a designed rate and to obtain its optimal blood concentration therapeutically. This property leads to the reduction of the administration frequency, which helps to increase patient compliance and prevent adverse effects (Table1).

Table 1 Benefit characteristics of oral sustained release formulations

Benefit Reason	
Therapeutic benefit	Reduce the fluctuations in drug plasma level; maintain a drug plasma level as the over a extended time period, ideally

	simulating an intravenous infusion of a drug
Reduce in adverse effects and enhance in tolerability	Drug plasma levels are maintained within a narrow therapeutic with no sharp peaks and with AUC of plasma concentration versus time curve comparable with total AUC from multiple dosing with immediate release dosage forms.
Patient convenience and compliance	Oral sustained release delivery is the most usual and suitable for patients, and reduce in the dosing frequency enhances compliance.
Reduce in healthcare cost	The total cost of therapeutics of the sustained release product compare with the immediate release product, sustained release product is lower than the immediate release product, the total cost in disease management also would be reduced.

In order to achieve the object, a variety of systems have been developed. Among them, because of simple composition and ease of manufacture, many studies have been conducted on a matrix system, in which active ingredients are dispersed in polymers which control the release rate.

The rate of drug release from swellable matrix depends on the drug concentration in the gel layer. For example, when swelling occurs with erosion, the thickness of the gel layer remains persistent and zero order release is achieved (Conte et al., 1988). The possible presence in the gel of a diffusion front, particularly the border between the gel layer and dissolved drug, can affect the drug transport (Colombo et al.,

1995). In addition, the swellable polymer may replace particles in the gel layer owing to extension of the polymer chains (Adler et al., 1999).

The easily sustained release tablets, each containing active ingredient (pharmaceutical or nutritional) together with polymers, can be prepared by adjusting a mixture of active ingredient, water soluble polymers (e.g.cellulose derivative (e.g.hydroxypropyl methylcellulose, methylcellulose, hydroxypropylcellulose, carboxymethylcellulose, etc.), synthetic water soluble polymers (e.g.polyvinylpyrrolidone, cross-linked polyvinylpyrrolidone, polyethylene oxide, etc.), polysaccharides (e.g.pullulan, dextran, etc.), etc.) and other excipients (e.g. lubricant, diluents etc.)(U.S. Pat. No. 4695497).

Ethyl cellulose (EC) is a stable, non-toxic, inert, compressible, hydrophobic polymer that has been widely used to prepared pharmaceutical solid dosage forms. Particularly, sustained release tablet formulations. The properties of sustained release formulation containing ethyl cellulose, consisting matrix tablets for both soluble and poorly soluble drugs (Shaikh et al., 1987), microcapsules (Jalsenjak et al., 1977), microspheres (Eldridge et al.; 1990Akbuga, 1991) and film coated tablets (Rowe, 1992) have been reported.

Hydroxypropyl methylcellulose (HPMC) is stable, non-toxic, relatively low cost, high compressibility is able to accommodate high levels of drug loading and the process variables show little effect on drug release (Ranga Rao and Padmalatha, 1988; Pham and Lee, 1994). Moreover, HPMC is available in many different viscosity grades, and four different degrees of substitution (e.g. E4M, K15M etc.) are pharmaceutical approved (United States Pharmacopeia USP30-NF25). HPMC has been widely used in hydrophilic matrix tablets with pharmaceutical dosage form (Alderman, 1984; Ranga Rao and Padmaklatha, 1988; Colombo et al., 2000; Siepmann and Peppas, 2001; Miller-Chou and Koenig, 2003; Kanjickal and Lopiona, 2004).

Xanthan gum has a high molecular weight extracellular polysaccharide, manufactured on commercial scale by the viscous fermentation of gram negative

bacterium *Xanthomonas campesteris*. The molecule composes of a backbone identical to that of cellulose, with side chains attached to alternate glucose residues. It is a hydrophilic polymer, which until recently had been limited for use in thickening, stabilizing, suspending and emulsifying water based systems (Gwen et al., 1996). It seem to be gaining evaluation for fabrication of matrix as it not only retards drug release, but also provides time-independent release kinetics with added advantages of biocompatibility and inertness. Release of soluble drugs was mainly through diffusion, whereas sparingly soluble or insoluble drugs were released through erosion. It is also recommended for use in both acidic and alkaline systems. Xanthan gum has been evaluated as a hydrophilic matrix for controlled release preparation, using different model drugs including theophylline (Fu et al., 1991), prednisolone (Watanabe et al., 1992), indomethacin (Watanabe et al., 1993) and cephalexin (Dhopeshwarkar et al., 1994).

Carrageenan is an anionic polymer extracted from marine red algae. Its structure is a linear heteropolysaccharide with ester sulfate groups. The main chain consists of alternative copolymer of 1,4-α and 1,3-β-D-galactopyranose and 3,6-anhydro-D-galactopyranose. Because of its gelling, suspending, viscosity enhancing, and proven safety properties (Gupta et al., 2001), carrageenan can be used as a sustained-release composition. For example, sustained release tablet matrix.

Sodium alginate is a natural hydrophilic polysaccharide derived from seaweed. The property of this polymer to rapidly form viscous solutions and gels on contact with aqueous media has been exploited by the pharmaceutical industry, its wide application as a carrier in hydrophilic matrix controlled release oral dosage forms, stabilizing, suspending and viscosity-increasing agent. Matrix is incorporating either a single alginate salt or the combination salts have been employed to successfully sustain release of many drugs in vitro and in vivo (Patric, 1984; Yie, 1992; Kathleen et al., 1996; Brahma et al., 2002).

Sodium alginate is the sodium salt of alginic acid (Kakkar, 1995), a high molecular weight linear random copolymer consisting of blocks of 1 ---> 4, linked D-mannuronic acid (MM) and L-guluronic acid residues (GG), in addition to regions in which the two uronic acid residues alternate (Mann, 1989; Martin, 1991; Alf et al., 2000; Dandagi, 2004). By adventage of the carboxyl groups on the component uronic acid residues, the pKa of alginic acid ranges between 3.4 and 4.4, depending on the type of alginate and the salts present in the mixture (Srinivas et al., 2008). Therefore, changes in pH over the region of pH 3 to 4, from more neutral pH values, influence polymer hydration and alginate gel rheology, due to the ready interconversion of carboxylate anions (sodium alginate) to free carboxyl groups (alginic acid), as the concentration of hydrogen ions increases (Ranga, 1989; Pralhad, 2004). At neutral pH sodium alginate is soluble and hydrates to form viscous solutions, but below pH 3, alginic acid, water swellable but insoluble, is rapidly formed. Since the hydration characteristics of the polymer and the subsequent physical properties of the hydrated gel layer may critically influence drug release (Rajesh et al., 2003), any change in the properties of the hydrated surface layer caused by a change in pH, is likely to influence the performance of sodium alginate as a sustained release carrier.

Manjanna et al. reported that the effect of pH on the release of two drugs of differing water-solubility from sodium alginate matrices. Cryogenic scanning electron microscopy (cryo-SEM) and liquid uptake studies were used to describe the pH-dependent differences observed in drug release, in terms of the internal microscopic structure of the gel layer and the hydration kinetics of the polymer.

Kollidon® SR is one of the recently developed matrix forming agents with plastic behavior. Chemically, Kollidon® SR is polyvinyl acetate and polyvinyl pyrrolidone based matrix retarding agent particularly appropriate for the manufacture of pH independent sustained release matrix tablets. Polyvinyl acetate is a very plastic material that produces a coherent mass even under low compression force. When the tablets prepared with Kollidon® SR are introduced into gastric or intestinal fluid, the water

soluble polyvinylpyrrolidone is leached out to form pores through which the active ingredients slowly diffuses outsides in a controlled and pre-determined fashion. Kollidon® SR contains no ionic groups that cause them inert to the drug molecule. Its high flowability, low reposition angle and excellent compressibility characteristics provide the tablets with required hardness and low friability while simultaneously reducing the process variables and processing cost (BASF, 1999).

Apurba, 2009 reported that theophylline was taken as the model drug to investigate various formulations of matrix tablets using Eudragit® RSPO and Eudragit® RLPO acrylic polymers. Eudragit® RS and Eudragit® RL have been used as rate retarding polymers for more than a decade. But their powder forms, Eudragit® RLPO and RSPO have free flowing and direct compressible properties are different from other forms.

Retardation of dissolution rate is achieved by incorporating the drug in an insoluble carrier such as ethyl cellulose, PEG , Eudragit® RSPO etc. such formulation are considered as a matrix system helps in prolonging the duration of time over which the drug is released and hence are considered suitable for formulation as sustained release dosage forms. It is found that different insoluble polymers like ethyl cellulose, Eudragit® RSPO etc., were attempted in designing of sustained release solid dispersions by using various solid dispersion techniques. Therefore, in the present investigation, it is aimed to study the suitability of using ethyl cellulose, Eudragit® RSPO, in the development of solid dispersion system for controlling the drug release rate (Samba et al., 2010).

Matrix tablets

These are many types of controlled release drug delivery systems, which release the drug in continuous manner. These release the drug by both dissolution controlled as well as diffusion controlled mechanisms. To control the release of the drugs, which are having different solubility properties, the drug is dispersed in swellable hydrophilic

substances, an insoluble matrix of rigid nonswellable hydrophobic materials or plastic materials.

Classification of matrix tablets

On the basis of retardant material used: matrix tablets can be divided in to 5 types.

1. Hydrophobic matrix (Plastic matrix)

The concept of using hydrophobic or inert materials as matrix materials was first introduced in 1959. In this method of obtaining sustained release from an oral dosage form, drug is mixed with hydrophobic polymer or inert and then compressed in to a tablet. Sustained release is prepared due to the fact that the dissolving drug has diffused through a network of channels that exist between compacted polymer particles.

The rate-controlling step in these formulations is liquid penetration into the matrix. The possible mechanism of release of drug in such type of tablets is diffusion. Such types of matrix tablets become inert in the presence of water and gastrointestinal fluid.

2. Lipid matrix

These matrices prepared by the lipid waxes and related materials. Drug release from such matrix occurs through both pore diffusion and erosion. Release characteristics are more sensitive to digestive fluid composition than to totally insoluble polymer matrix.

3. Hydrophilic matrix

The formulation of the drugs in gelatinous capsules or more frequently, in tablet, using hydrophilic polymers with high gelling capacities as base excipients, is of particular interest in the field of sustained release. Affect a matrix is determined as well

mixed compound of one or more drugs with a gelling agent (hydrophilic polymer). These systems are called swellable controlled release systems.

4. Biodegradable matrix

These consist of the polymers which comprise monomers linked to one another through functional groups and have unstable linkage in the backbone. They are biologically degraded or eroded by enzymes generated by surrounding living cells or by nonenzymetic process in to olegomers and monomers that can be metabolised or excreted.

5. Mineral Matrix

These compose of polymers which are obtained from various species of seaweeds. For example, alginic acid which is a hydrophilic carbohydrate obtained from species of brown seaweeds (Phaephyceae) by the use of dilute alkali.

Advantages of Matrix Tablets

1. Easy to manufacture
2. Versatile, effective and low cost
3. Can be prepared to release high molecular weight compounds

Disadvantages of the matrix systems

1. The remaining matrix must be removed after the drug has been released.
2. The drug release rates vary with the square root of time. Release rate continuously decrease due to an increase in diffusional resistance and/or a decrease in effective area at the diffusion front. However, a substantial sustained effect can be produced through the use of very slow release rates, which in many applications are indistinguishable from zero-order.

Multilayer sustained release tablet

Multilayer tablets, particularly those including hydrophobic excipients and/or swellable excipients, are useful in administering hygroscopic and/or deliquescent drugs. In addition, varying the amount of drug in multilayer tablets allows the release rate of the drug to be controlled (Nangia et al., 2008).

An oral multilayer sustained release tablet, more particularly, a multilayer tablet composing of an inner immediate-release layer containing a pharmaceutically active ingredient and two outer layers containing swelling polymers. On exposure to aqueous media, the two outer layers swell to form gelled layers surrounding the lateral side of the inner layer rapidly as shown in Figures 3-4, which control effectively the releases of drug from the inner immediate-release layer (Park et al., 2010).

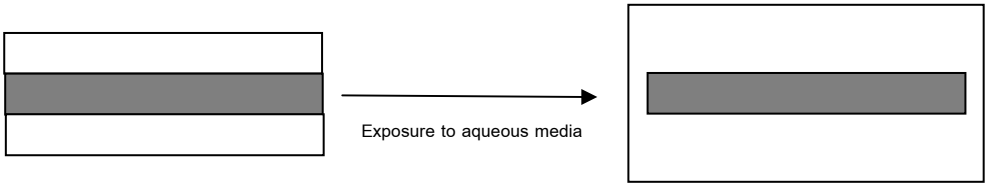


Figure 3 An oral multilayer sustained release tablet, composing of an inner layer containing a pharmaceutical active ingredient, outer layer containing swellable polymer (From Park et al., 2010)

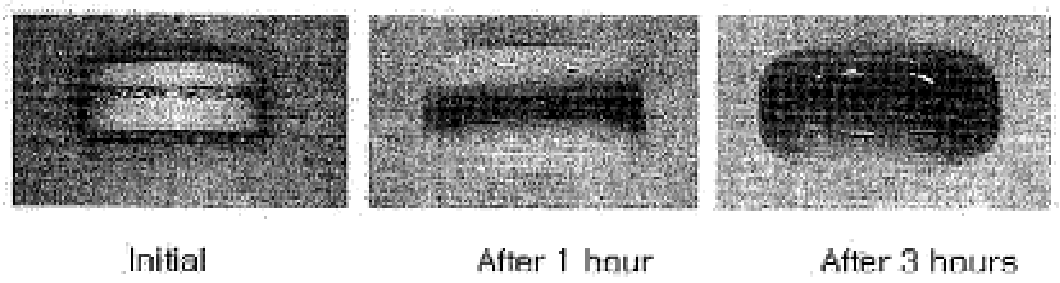


Figure 4 The results of the stirring and gelling test of Figure 4 (From Park et al., 2010)

A multilayer oral dosage form that provides controlled release of an active ingredient includes a core layer containing a pharmaceutical active ingredient and/or a nutritionally active ingredient, and at least one release-modulating layer laminate to each side of the core layer. The dosage form can be prepared using simple, inexpensive tablet compression techniques.

Zerbe et al, 2007 reported that a multilayer oral dosage form that includes a non-erodible core containing a pharmaceutical active ingredient and/or nutritionally active ingredient and at least one release-modulating layer laminated to each side of the core layer as shown in Figure 5. The resulting multilayer oral dosage form is a diffusion-controlled device that contains an active ingredient distributed through and insoluble matrix in the proximity of the exposed surface, the drug release rate becomes a function of diffusion path length through the insoluble matrix.

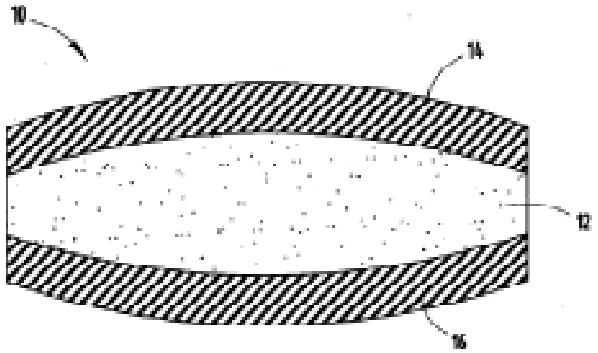


Figure 5 Cross section view of a trilayer tablet, 10 of this invention comprise at least three layers, including a non-erodible layer 12 and which is sandwiched between at least two additional layers 14, 16. (From Zerbe et al, 2007)

Sustained release tablet of sodium valproate combined with valproic acid

Sodium valproate (2-propylpentanoic acid sodium salt) is a useful drug widely employed for treatment of epilepsy and prevention ictus epilepticus. The effective blood concentration of the drug generally ranges from 50 to 100 μg/ml. Because sodium valproate has a short biological half-life, sodium valproate must be administered three or four times a day to maintain an effective blood concentration. Since such a short dose interval is troublesome for patients, there have been many efforts to develop long-acting, sustained release preparation of sodium valproate.

However, sodium valproate should be administered at a relatively high daily dose approaching 1200 mg. Moreover, sodium valproate is highly hygroscopic. Hence, conventional sustained release tablets compose a relatively large proportion of adjuvants, such as retarders, and therefore are unsatisfactorily weighty and bulky. Techniques for preparing sustained release tablets of sodium valproate include (a) a process comprising mixing valproic acid and (b) a process comprising preparing by the incorporation of the drug in a matrix containing a rate-controlling polymer (Ukigaya et al., 1996).

The sustained release tablets obtained by process (a) are pH sensitive. Therefore, the rate of drug dissolution varies with the pH in the various portions of the digestive tract and thus the blood concentration is sensitive to wide variation (b) do not maintain the optimal blood concentration, with the concentration decreasing considerably after 10 hours of administration. The sustained release tablets obtain by process.

Sodium valproate and valproic acid have been used in combination because there are minor differences in the pharmacokinetics of the formulation and accessibility in market (Lin et al., 2004). Sodium valproate and valproic acid are available in different dosage forms; tablet, enteric-coated tablet, capsule, sprinkle, liquid, intravenous, suppository and controlled release formulations (Loscher et al., 1999). Sustained release formulation of the combination between sodium valproate and valproic acid reduces the

fluctuation in plasma drug concentrations, thus minimizing or preventing plasma peak-related adverse events, and allows prolongation of the dosing interval enabling a once or twice daily administration with inherent benefits in terms of patient compliance (Doughty et al., 2003).

Valproic acid is liquid at room temperature and thus not appropriate for manufacturing of solid dosage forms, e.g., tablets for oral administration. Sodium valproate is solid, but an extremely hygroscopic, deliquescent substance. It absorbs water from the atmosphere already during tabletting, resulting in problems of tablet production, like sticking to the punches (Holzkirchen, 1999). A valproic acid-sodium valproate 1:1 complex (divalproex sodium) is described in U.S. Pat. No. 5,212,326 and WO 96/23491. It is a solid at room temperature and is described to be nonhygroscopic.

Nangia, et al 2008 reported that sodium valproate bioadhesive tablet formulations, base on the concentretion gradient approach, were prepared. Tablets from the first lot utilized L-Dopa/BMA (Spheromer™III) as the bioadhesive polymer while tablets from the second lot were based on p (FA:SA) bioadhesive polymer. An additional tablet lot using ethylcellulose as a non-bioadhesive polymer was also prepared. Figure 6 presented an illustrastration of trilayer tablet with a bioadhesive coating.

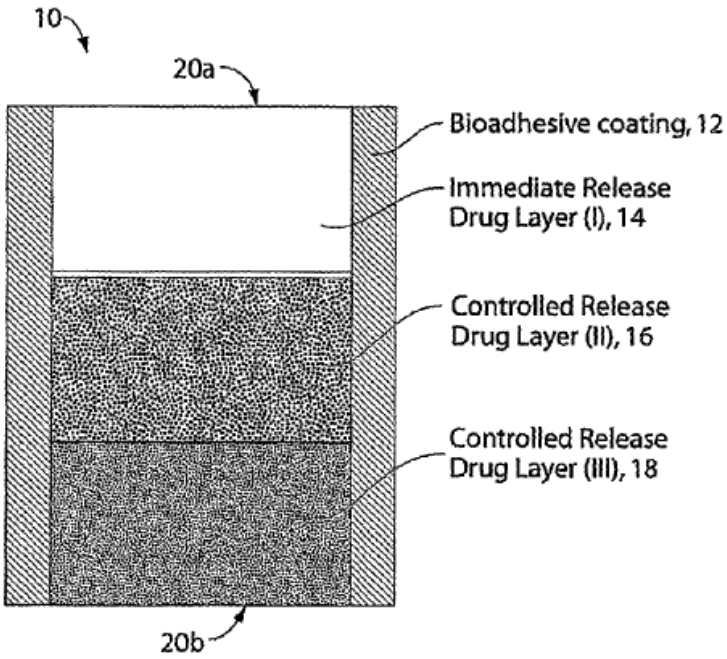


Figure 6 10 is an illustrastration of trilayer tablet with a bioadhesive coating 12, immediate release drug layer 14, controlled drug layer 16, controlled drug layer 18 and two additional layers 20a, 20b. (From Nangia et al., 2008)

Kumar et al, 2004 studied on extended release pharmaceutical composition comprising 10-90% of divalproex sodium, 7-65% of hydroxypropyl methylcellulose, 0.5-18% of lactose and 0.5-5% of colloidal silicon dioxide wherein all percentages are based upon the total weight of the pharmaceutical composition and it is manufactured at temperature about 27-35 °C and humidity of less than 20%.

Quantitative analysis of sodium valproate in tablet dosage form

Sodium valproate is official in BP and USP but these pharmacopoeias have adopted gas chromatography (GC) method for quantitative analysis of this drug in formulation. There are number of analytical methods reported in recent pharmaceutical literature for the quantification of sodium valproate in biological matrix either alone or in combination with other drugs. These include high performance liquid chromatography (HPLC) with MS detection (Deepak et al., 2007; Tsukasa et al., 2007), UV detection

(Gupta et al., 2009) and fluorescence detection (Yan et al., 2006), isotope-dilution mass spectrometry (Susanto and Reinauer, 1995), and gas chromatography (Pravin et al., 2006).

Only a few high-performance liquid chromatographic (HPLC) methods have been reported for the analysis of sodium valproate because sodium valproate lacks nitrogen and a ring moiety and therefore has no chromophoric characteristics (Kushida et al., 1985). HPLC methods with UV detection at 210 nm (Lovett et al.,1987; Gupta et al., 2009) and 220 nm (Victoria et al., 2010) are available for sodium valproate and valproic acid based on deproteination with acetonitrile, which in turn leads to decreased sensitivity and selectivity.

Kinetic analysis of dissolution profiles

The kinetic analysis of dissolution profiles has been attempted using different release models. Drug release data were fitted to kinetic model including:

Zero order: $M_t = M_o + K_o t$

First order: $\ln M_t = \ln M_o + K_1 t$

Higuchi model: $M_t = K_H \sqrt{t}$

To estimate the mechanism of drug release data were fitted in Korsmeymer-Peppas model:

Korsmeyer-Peppas model: $M_t/M_o = K_k t^n$

M_t = amount of drug dissolved in time t

M_o = initial amount of drug

K_1 = first order release constant

K_o = zero order release constant

K_H = Higuchi rate constant

K_k = release constant

n = diffusional release exponent indicative of the operating release mechanism.

Table 2 Release exponent values in Korsmeyer–Peppas model

Diffusion exponent (n)			Drug release mechanism
Slap	Cylinder	Sphere	
0.5	0.45	0.43	Fickian diffusion
0.5<n<1.0	0.45<n<0.89	0.43<n<0.85	Non Fickian diffusion
1.0	0.89	0.85	Case II transport
n>1.0	n>0.89	n>0.85	Super case II transport

The coefficient of determination (R^2) was used as an indicator of the best fitting for each of the models considered.

CHAPTER III
MATERIALS AND METHODS

1. Materials

1.1 Active ingredients

Sodium valproate (Lot. number 20100201, Supplied by Atlantic, Thailand)

Valproic acid (Batch number 440752, Katwijk chemie BV, Netherland)

1.2 Excipients

Ethylcellulose (CAS number 9004-57-3, Shandong, China)

Hydroxypropyl methylcellulose E4M (Methocel E4M, Lot. number PD 300915, DOW Chemical, USA)

Hydroxypropyl methylcellulose K15M (Methocel K15M, Lot. number PD 300936, DOW Chemical, USA)

Xanthan gum (CAS number 1138-66-2, Xingji Bang Na Trade, China)

Carrageenan (Batch number 20100105, Zhengzhou, Henan, China)

Sodium alginate (Lot. number DY070704, Topflight interfoods, Bangkok, Thailand)

Kollidon® SR (Lot. number 65130468EO, BASF, Germany)

Eudragit® RSPO (Lot. number G031038154, Degussa, Germany)

Dibasic calcium phosphate (Lot. number 5F/269, Sudeep Pharma, India)

Colloidal silicon dioxide (Lot. number ZB55869, Wacker, Germany)

Veegum (Lot. number 9074, Unique Pharmaceuticals, India)

Talcum (Lot. number 21546-024599, Liaoning Metais and Minerals, China)

Polyvinyl pyrroridone (PVPK90, CAS number 9003-39-8, Batch 200901008, Nanhang Industrial, China)

Ethyl alcohol (Absolute alcohol AR quality, Batch number 10/649 A3F200311, Heyman, England)

1.3 Solvents for HPLC

Trifluoroacetic acid (CAS number 76-05-1, Sigma-Aldrich, Singapore)

Orthophosphoric acid (Batch number 1003346, Ajax Finechem, Australia)

Potassium dihydrogen orthophosphate (Batch number F2H145, Ajax Finechem, Australia)

Acetonitrile (Matl. number 10071743, Burdick & Jackson, B&J ACS HPLC Certified solvent, SK chemicals, Korea)

Methanol (Matl. number 10071753, Burdick & Jackson, B&J ACS HPLC Certified solvent, SK chemicals, Korea)

Ultrapure water

1.4 Chemicals for dissolution

Potassium dihydrogen orthophosphate (Batch number F2H145, Ajax Finechem, Austrelia)

Sodium hydroxide (Lot. number B231098 243, Merck, Germany)

Hydrochloric acid (Lot. number K41831617 101, Merck, Germany)

Potassium cloride (Batch number AF501338, Ajax Finechem, Australia)

Deionized water

1.5 Apparatus

Hydrulic tablet machine (CARVER® hydraulic press, Wabash, Indiana, USA)

Punch and die (caplet) (Jaraschai Machinery, Bangkok, Thailand)

Thickness tester (Teclock SM-112, Japan)

Hardness tester (Thermonik model DHT-250)

Friability tester (Erweka, Western Germany)

Dissolution apparatus (model VK7000, Vankel, U.S.A.)

High performance liquid chromatography machine (Shimadzu, binary pump: LC-20AB, autosampler: SIL-20A HT, Detector: SPD-20A, computer: Compaq)

2. Methods

2.1 Development of analytical method for determination of drug by high performance liquid chromatography (HPLC)

2.1.1 Chromatographic condition of HPLC analysis

Chemical content of the sodium valproate tablets was analysed using a high performance liquid chromatography (HPLC) method, coupled to a UV detector set to 210 nm. The HPLC system consisted of a binary pump system (Shimadzu, LC-20AB), autosampler (Shimadzu, SIL-20A HT) and UV/VIS detector (Shimadzu, SPD-20A). A reverse-phase Inertsil ODS3 C-18 column 4.6 x 250 mm was eluted by using a mixture (60:40) of acetronitrile and 0.05% trifluoroacetic acid as the mobile phase with a flow rate was set to 1 ml/min and the injection volume was 20 µl (Table 3). Analyses were conducted at ambient laboratory temperature (26 ± 1.5°C). Validation parameters of linearity, accuracy, precision and standard and sample solution stability were confirmed for this method.

Table 3 Chromatographic condition of HPLC analysis

Column	reverse-phase Inertsil ODS3 C-18 column 4.6 x 250 mm
Mobile phase	Acetronitrile : 0.05% trifluoroacetic acid (60 : 40 v/v)
Flow rate	1 ml per minute
Detector	UV detector 210 nm
Injection volume	20 µl

2.1.2 Validation method of HPLC analysis

2.1.2.1 Stock standard preparation

The mobile phase was used as diluent. About 50 mg of sodium valproate working standard was weighed accurately in 50 ml volumetric flask and mobile phase was added, sonicated to dissolve and diluted to the mark to obtain a concentration of 1 mg/ml.

2.1.2.2 Linearity of HPLC

Linearity was studied by preparing standard solutions at different concentration levels such as 0.2, 0.4, 0.6, 0.8 and 1.0 mg/ml. The data were plot as area versus drug concentration (mg/ml).

2.1.2.3 Accuracy of HPLC

To ensure the accuracy and reliability of the method, recovery studies were carried out in triplicate at three concentration levels (50%, 100% and 150%) of test concentration.

2.1.2.4 Precision of HPLC

The intra-day precision of the assay method was evaluated by carrying out six independent assays of sodium valproate (1000 µg/ml) test samples against qualified reference standard on same day and these studies were also repeated on six consecutive days to determine inter-day precision. The percentage of RSD of six assay values was calculated.

2.1.2.5 Sample solution stability

The solution stability of sodium valproate was carried out by leaving the test solutions in a tightly capped volumetric flask at room temperature for 120 hours. The relative standard deviation was not more than 2.0 %.

2.2 Selection of adsorbent

Sodium valproate is a highly hygroscopic nature, its formulations often poses problem during production and storage. Veegum and colloidal silicon dioxide were individually tested for sodium valproate adsorption by mixing with excipients as shown in Table 4. The effect of adsorbent on physical properties of matrix tablets was visually observed and chosen a better adsorbent for the next experiment.

Table 4 Formula of sodium valproate matrix tablet

Ingredient	Formulation (weight per tablet; mg)				
	1	2	3	4	5
Sodium valproate	230	230	230	230	230
Ethylcellulose	20	20	20	20	20
Dibasic calcium phosphate	138	128	118	128	118
Colloidal silicon dioxide	-	-	-	10	20
Veegum	-	10	20	-	-
Talcum	12	12	12	12	12
Total weight (mg)	400	400	400	400	400

All the formulations were composed of 230.0 mg of sodium valproate (equivalent to valproic acid 200 mg), 20.0 mg of ethylcellulose and 12.0 mg of Talcum and required amount of dibasic calcium phosphate as diluent. The varied absorbents were: no absorbent, veegum and colloidal silicon dioxide at the concentration of 2.5% and 5.0% by weight and the amount of dibasic calcium phosphate was decreased as the concentration of polymer was increased. All ingredients were mixed and compressed by direct compression at 3000 psi using a CARVER® hydraulic press. Humidity in the room was controlled to be lower than 50%RH.

2.3 Effect of preparation method on drug release from sodium valproate matrix tablet

2.3.1 Direct compression method

Table 5 Formula of sodium valproate matrix tablet

Ingredient	weight per tablet; mg
Sodium valproate	230
Ethylcellulose	20
Dibasic calcium phosphate	118
Colloidal silicon dioxide	20
Talcum	12
Total weight (mg)	400

The formulation was composed of 230.0 mg of sodium valproate (equivalent to valproic acid 200 mg), 20.0 mg of ethylcellulose, 118 mg of dibasic calcium phosphate, 20.0 mg of colloidal silicon dioxide and 12.0 mg of Talcum as shown in Table 5. All ingredients were mixed and compressed by direct compression at 3000 psi using a CARVER® hydraulic press. Humidity in the room was controlled to be lower than 50%RH. Amount of drug release from matrix tablets were analyzed by validated HPLC method.

2.3.2 Wet granulation method

Table 6 Formula of sodium valproate matrix tablet

Ingredient	weight per tablet; mg
Sodium valproate	230
Ethylcellulose	20
Dibasic calcium phosphate	118
Colloidal silicon dioxide	20
Talcum	12
PVP K90	qs.
Total weight (mg)	400

The formulations was composed of 230.0 mg of sodium valproate (equivalent to valproic acid 200 mg), 20.0 mg of ethylcellulose, 118 mg of dibasic calcium phosphate, 20.0 mg of colloidal silicon dioxide, 12.0 mg of Talcum and 5%w/w PVP K90 in 95% ethyl alcohol as shown in Table 6.

Wet granules were prepared by adding PVP K90 in 95% ethyl alcohol solution (5% w/w of total weight of matrix tablet formulation) into mixture of sodium valproate and ethylcellulose, sheared by the pestle and screened through a 16-mesh sieve. The granules were tray dried at 60° using a hot air oven for 30 minutes. The dried granules were screened through a 18-mesh sieve. Granules were stored in dessicator throughout the preparation. Other ingredients were mixed and compressed by direct compression at 3000 psi using a CARVER® hydraulic press. Humidity in the room was controlled to be lower than 50%RH. Amount of drug release from matrix tablets were analyzed by validated HPLC method.

Because of unsuitable method of wet granulation, direct compression method was chosen for developing sodium valproate matrix tablet.

2.4 Effect of different polymers on drug released from sodium valproate matrix tablet by direct compression method

All the formulations were composed of 230.0 mg of sodium valproate (equivalent to valproic acid 200 mg), 20.0 mg of colloidal silicon dioxide and 12.0 mg of talcum and required amount of dibasic calcium phosphate as diluent. The polymer used in the matrix tablets were : ethylcellulose, HPMC E4M, HPMC K15M, xanthan gum, carrageenan, sodium alginate, Kollidon® SR, Eudragit® RSPO at the concentration of 5%, 10%. 15% and 20% by weight. The amount of dibasic calcium phosphate was decreased as the concentration of polymer was increased as shown in Table 7. All ingredients were mixed and compressed by direct compression at 3000 psi using a CARVER® hydraulic press. Humidity in the room was controlled to be lower than 50%RH. Amount of drug release from matrix tablets were analyzed by validated HPLC method.

Table 7 Formula of sodium valproate matrix tablet

Ingredient	Formulation (weight per tablet; mg)			
	1	2	3	4
Sodium valproate	230	230	230	230
Ethylcellulose	20	40	60	80
Dibasic calcium phosphate	118	98	78	58
Colloidal silicon dioxide	20	20	20	20
Talcum	12	12	12	12
Total weight (mg)	400	400	400	400
Ingredient	**Formulation (weight per tablet; mg)**			
	1	2	3	4
Sodium valproate	230	230	230	230
HPMC E4M	20	40	60	80
Dibasic calcium phosphate	118	98	78	58
Colloidal silicon dioxide	20	20	20	20

Talcum	12	12	12	12
Total weight (mg)	400	400	400	400
Ingredient	**Formulation (weight per tablet; mg)**			
	1	**2**	**3**	**4**
Sodium valproate	230	230	230	230
HPMC K15M	20	40	60	80
Dibasic calcium phosphate	118	98	78	58
Colloidal silicon dioxide	20	20	20	20
Talcum	12	12	12	12
Total weight (mg)	400	400	400	400
Ingredient	**Formulation (weight per tablet; mg)**			
	1	**2**	**3**	**4**
Sodium valproate	230	230	230	230
Xanthan gum	20	40	60	80
Dibasic calcium phosphate	118	98	78	58
Colloidal silicon dioxide	20	20	20	20
Talcum	12	12	12	12
Total weight (mg)	400	400	400	400
Ingredient	**Formulation (weight per tablet; mg)**			
	1	**2**	**3**	**4**
Sodium valproate	230	230	230	230
Carrageenan	20	40	60	80
Dibasic calcium phosphate	118	98	78	58
Colloidal silicon dioxide	20	20	20	20
Talcum	12	12	12	12
Total weight (mg)	400	400	400	400
Ingredient	**Formulation (weight per tablet; mg)**			
	1	**2**	**3**	**4**
Sodium valproate	230	230	230	230
Sodium alginate	20	40	60	80

Dibasic calcium phosphate	118	98	78	58
Colloidal silicon dioxide	20	20	20	20
Talcum	12	12	12	12
Total weight (mg)	400	400	400	400
Ingredient	**Formulation (weight per tablet; mg)**			
	1	**2**	**3**	**4**
Sodium valproate	230	230	230	230
Kollidon® SR	20	40	60	80
Dibasic calcium phosphate	118	98	78	58
Colloidal silicon dioxide	20	20	20	20
Talcum	12	12	12	12
Total weight (mg)	400	400	400	400
Ingredient	**Formulation (weight per tablet; mg)**			
	1	**2**	**3**	**4**
Sodium valproate	230	230	230	230
Eudragit® RSPO	20	40	60	80
Dibasic calcium phosphate	118	98	78	58
Colloidal silicon dioxide	20	20	20	20
Talcum	12	12	12	12
Total weight (mg)	400	400	400	400

Among the eight polymer used in the matrix tablets, ethylcellulose, HPMC E4M, xanthan gum, carrageenan, sodium alginate, Kollidon® SR and Eudragit® RSPO were not proved to be a sustaining polymer for sodium valproate matrix tablets, whereas HPMC K15M showed sustained action. Therefore, HPMCK15M were chosen for preparation of core matrix tablet.

2.5 Preparation and evaluation of matrix tablets

2.5.1 Preparation of core matrix tablet

Followed 2.4, the formulation was composed of 230.0 mg of sodium valproate (equivalent to valproic acid 200 mg), 20.0 mg of colloidal silicon dioxide, 12.0 mg of talcum, 118.0 mg of dibasic calcium phosphate and 20.0 mg of HPMC K15M. All ingredients were mixed and compressed by direct compression at 3000 psi using a CARVER® hydraulic press. Humidity in the room was controlled to be lower than 50%RH. The matrix tablet was evaluated for drug release and amount of drug release were obtained using validated HPLC method.

The formulation was stored in airtight containers at room temperature for study further (Saiful Islam et al., 2010).

2.5.2 Design of bilayer tablet

Effect of different polymers used in the outer layer on drug release from sodium valproate matrix

The formulation from 2.5.1 was used for design of bilayer tablet. The formulation was composed of 200.0 mg of ethylcellulose and HPMC K15M as a first layer in formulation 1 and 2, respectively. The second layer composed of 230.0 mg of sodium valproate (equivalent to valproic acid 200 mg), 20.0 mg of colloidal silicon dioxide, 12.0 mg of Talcum, 118.0 mg of dibasic calcium phosphate and 20.0 mg of ethylcellulose and HPMC K15M in formulation 1 and 2, respectively as shown in Table 8.

Bilayer tablets were compressed on a CARVER® hydraulic press using capsule shape punch-die set. First 200 mg of first layer was added to die cavity and pre-compressed, then 400 mg of second layer was added and compressed at 3000 psi for 1 second (Nangia et al., 2008).

Table 8 Formula of sodium valproate bilayer tablet

Ingredient	Formulation (weight per tablet; mg)			
	1		2	
Layer	First	Second	First	Second
Sodium valproate	-	230	-	230
Ethylcellulose	200	20	-	-
HPMC K15M	-	-	200	20
Dibasic calcium phosphate	-	118	-	118
Colloidal silicon dioxide	-	20	-	20
Talcum	-	12	-	12
Total weight (mg)	200	400	200	400
Total per tablet (mg)	600		600	

HPMC K15M as the rate outer layer was successfully prepared to achieve slow release of sodium valproate, a highly water-soluble drug. However, further development was required to obtain more prolonged release of sodium valproate from the system such as multilayer sustained release tablet.

2.5.3 Design of mutilayer sustained release tablet of sodium valproate

The formulation was composed of 200.0 mg of HPMC K15M as outer layers. The inner layer composed of 230.0 mg of sodium valproate (equivalent to valproic acid 200 mg), 20.0 mg of colloidal silicon dioxide, 12.0 mg of Talcum, 118.0 mg of dibasic calcium phosphate and 20.0 mg of HPMC K15M as shown in Table 9.

Trilayer tablets were compressed on a CARVER® hydraulic press using capsule shape punch-die set. First 200 mg of outer layer was added to die cavity and pre-compressed, then 400 mg of inner layer blend was added to the die cavity and pre-compressed again, and finally the 200 mg of outer layer was added and compressed at 3000 psi for 1 second (Nangia et al., 2008).

Table 9 Formula of mutilayer sustained release tablet of sodium valproate

Ingredient	weight per tablet (mg)		
	Outer layer	Inner layer	Outer layer
Sodium valproate	-	230	-
HPMC K15M	200	20	200
Dibasic calcium phosphate	-	118	-
Colloidal silicon dioxide	-	20	-
Talcum	-	12	-
Weight of each layer (mg)	200	400	200
Total weight per tablet	800		

2.5.4 Preparation of mutilayer sustained release tablet of sodium valproate for comparison with mutilayer sustained release tablet of sodium valproate combined with valproic acid and commercial product

From the previous experiment, the study was selected a suitable polymer on drug release from core matrix tablet, bilayer tablet and trilayer tablet. But in this experiment, the study was to compare dissolution profile with commercial product that contained sodium valproate combined with valproic acid 200 mg (equivalent to sodium valproate 200 mg). Therefore, reduced amount of sodium valproate to 200 mg.

The formulation was composed of 200.0 mg of HPMC K15M as outer layers. The inner layer composed of 200.0 mg of sodium valproate (equivalent to valproic acid 200 mg), 20.0 mg of colloidal silicon dioxide, 12.0 mg of Talcum, 148.0 mg of dibasic calcium phosphate and 20.0 mg of HPMC K15M as shown in Table 10. Trilayer tablets were compressed followed 2.5.3

Table 10 Formula of mutilayer sustained release tablet of sodium valproate

Ingredient	weight per tablet (mg)		
	Outer layer	Inner layer	Outer layer
Sodium valproate	-	200	-
HPMC K15M	200	20	200
Dibasic calcium phosphate	-	148	-
Colloidal silicon dioxide	-	20	-
Talcum	-	12	-
Weight of each layer	200	400	200
Total weight per tablet	800		

2.5.5 Design of multilayer sustained release tablets of sodium valproate combined with valproic acid

The formulation was composed of 200.0 mg of HPMC K15M as outer layers. The inner layer composed of 133.2 mg of sodium valproate, 58.0 mg of valproic acid, 40.0 mg of colloidal silicon dioxide, 12.0 mg of Talcum, 136.8 mg of dibasic calcium phosphate and 20.0 mg of HPMC K15M as shown in Table11.

Valproic acid was adsorped by adding colloidal silicon dioxide into valproic acid, sheared by the pestle and mixed with all ingredient. Trilayer tablets were compressed on a CARVER® hydraulic press using capsule shape punch-die set. First 200 mg of outer layer was added to die cavity and pre-compressed, then 400 mg of inner layer blend was added to the die cavity and pre-compressed again, and finally the 200 mg of outer layer was added and compressed at 3000 psi for 1 second (Nangia et al., 2008).

Table 11 Formula of multilayer sustained release tablets of sodium valproate combined with valproic acid

Ingredient	weight per tablet (mg)		
	Outer layer	Inner layer	Outer layer
Sodium valproate	-	133.2	-
Valproic acid	-	58	-
HPMC K15M	200	20	200
Dibasic calcium phosphate	-	136.8	-
Colloidal silicon dioxide	-	40	-
Talcum	-	12	-
Weight of each layer	200	400	200
Total weight per tablet	800		

2.6 Physical properties of multilayer sustained release tablets of sodium valproate and multilayer sustained release tablets of sodium valproate combined with valproic acid

2.6.1 Weight

Twenty tablets of each formulation were individually weighted using an analytical balance.

2.6.2 Thickness

Ten tablets of each formulation were individually weighted using a thickness tester

2.6.3 Hardness

Ten tablets of each formulation were individually weighted using a hardness tester

2.6.4 Friability

Weight ten tablets (W_0), place in a rotating drum for 100 times and remove any loose dust and reweight (W). The friability (*f*) is calculated from:

$$f\,(\%) = 100 \times [1-(W/W_0)]$$

2.7 Dissolution studies

For the dissolution study of matrix tablets and bilayer tablets, USP apparatus I (basket) dissolution tester, operating at 100 rpm was used. Dissolution test was performed in 900 ml of deionized water. While dissolution test for 24 hours of multilayer tablets of sodium valproate and those of sodium valproate combined with valproic acid were performed in 900 ml of 0.1 N HCl, phosphate buffer pH 6.8 and pH change (0.1 N HCl for 2 hours followed by phosphate buffer pH 6.8 for 22 hours), the medium temperature was maintained as 37±0.5 °C. Ten mililiters of dissolution medium was withdraw at 15, 30 min and every 1 hour until 24 hours. The medium was replenished with ten millimeters of fresh buffer each time. Each sample was filtered through 0.45 µm Nylon filter. 20 µl of each from these samples were injected into the chromatograph by autosampler and peak areas were measured.

2.8 Kinetic analysis of dissolution profiles of multilayer sustained release tablets of sodium valproate, multilayer sustained release tablets of sodium valproate combined with valproic acid, Depakine chrono® and Encorate chrono®

The kinetic analysis of dissolution profiles has been attempted using different release models. Drug Release data were fitted to kinetic model including the zero-order (cumulative amount of drug release versus time), first-order (log cumulative % of drug remaining versus time), Higuchi (cumulative % of release versus square root of time) and Korsmeymer-Peppas (log cumulative % drug release verses log time).

CHAPTER IV
RESULTS AND DISCUSSION

1. Development of analytical method for determination of drug by high performance liquid chromatography (HPLC)

Sodium valproate is official in BP and USP but these pharmacopoeias have adopted gas chromatography (GC) method for quantitative analysis of this drug in formulations. There are number of analytical methods reported in recent pharmaceutic literature for the quantification of sodium valproate in biological matrix either alone or in combination with other drugs. These include high performance liquid chromatography (HPLC). The chromatogram of sodium valproate is presented in Figure 7.

To determine the specificity of the analytical method, placebo solution and sodium valproate solution dissolve in the same solvent. Both solutions were filtered through 0.45 µm Nylon filter. Equal volumes (20 µl) of each sample were injected into the chromatograph by autosampler and peak areas were measured. The chromatogram of placebo was compared with the chromatogram of sodium valproate. As a result, the chromatogram of placebo was not shown the peak area at 7.665 minutes.

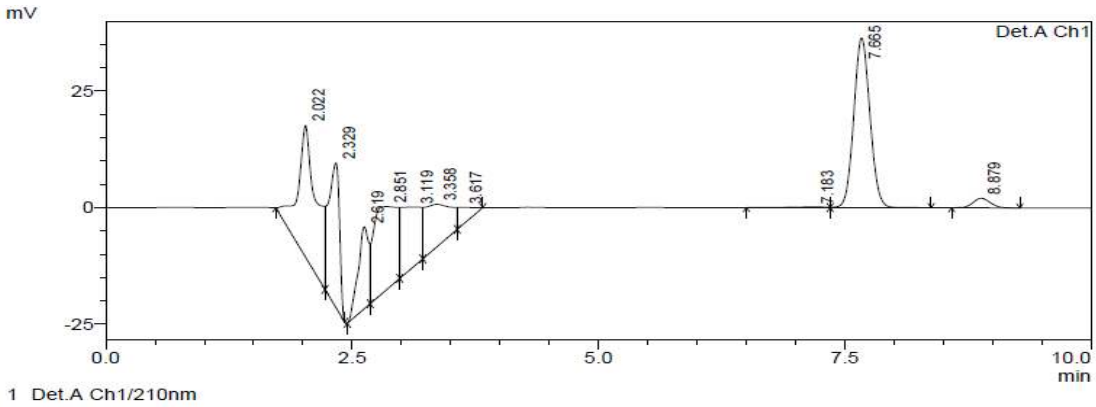


Figure 7 The chromatogram of sodium valproate (retention time 7.665 minutes)

Validation method of HPLC analysis

The proposed method was validated for assay of sodium valproate using following parameters.

1.1 Linearity

Linearity was studied by preparing standard solutions at different concentration levels. When the concentrations of sodium valproate and its respective peak areas were subjected to regression analysis by least squares method, a good linear relationship (R^2 = 0.9999) was observed between the concentrations of sodium valproate and the respective peak areas in the range 0.2-1.0 mg/ml (Figure 8). The regression equation was found to be y = *705745 x - 1965.6*, where Y is the peak area and X is the concentration of sodium valproate.

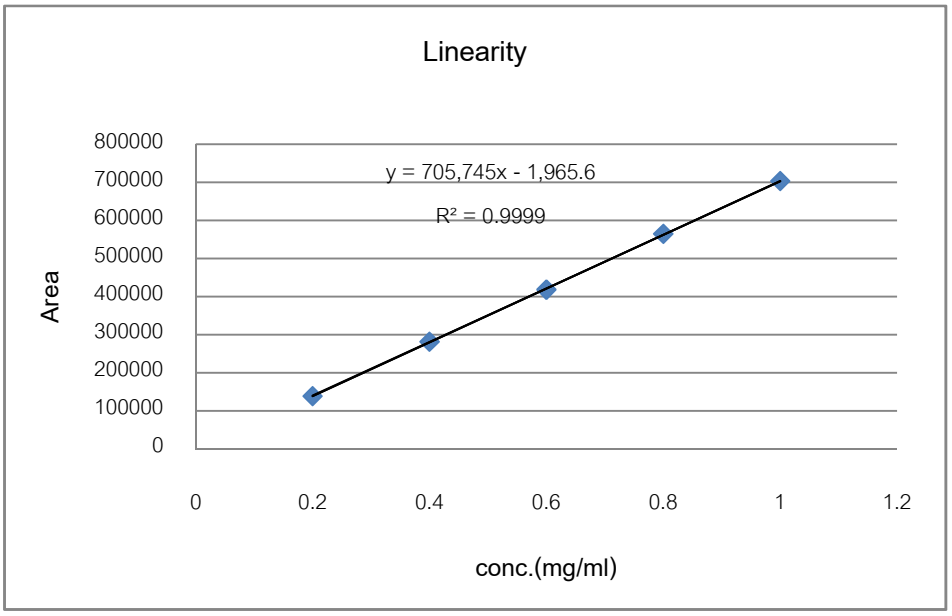


Figure 8 Linearity of sodium valproate determined at 210 nm

1.2 Accuracy

To ensure the accuracy and reliability of the method, recovery studies were carried out in triplicate at three concentration levels (50%, 100% and 150%) of test concentration. The recovery of sodium valproate was found to be in the range of 98.04-101.02 % (Table 12).

Table 12 Accuracy of HPLC

Level (%)	Drug added (mg)	Drug recovered (mg)	%RecoveryMean (n=3)	%RSD of assay (n=3)
50	143.75	145.21	101.02	0.26
100	287.50	282.22	98.16	0.24
150	431.25	422.79	98.04	0.30

1.3 Precision

The intra-day precision of the assay method was evaluated by carrying out six independent assays of sodium valproate (1000 µg/ml) test samples against qualified reference standard on same day and these studies were also repeated on six consecutive days to determine inter-day precision. The percentage of RSD of six assay values was calculated. Results are shown in Table 13.

Table 13 Precision of HPLC

Concentration (µg/ml)	Intra-day precision		Inter-day precision	
	%Assay	%RSD of assay	%Assay	%RSD of assay
1000	99.66	0.46	99.85	0.06

1.4 Sample solution stability

The sample solution stability of sodium valproate was carried out by leaving the test solutions in a tightly capped volumetric flask at room temperature for 120 hours. The same sample solutions were assayed for a 6 hours interval up to the study period against freshly prepared solutions. The relative standard deviation was found below 2.0 %. It showed that both standard and sample solutions were stable up to 120 hours at room temperature. Results are shown in Table 14.

Table 14 Sample solution stability

Concentration (µg/ml)	Intra-day precision		Inter-day precision	
	%Assay	%RSD of assay	%Assay	%RSD of assay
1000	99.01	0.22	99.01	0.24

2. Selection of adsorbent

Veegum and colloidal silicon dioxide were individually tested for sodium valproate adsorption by mixing with excipients at the concentration of 2.5% and 5.0% by weight and compared with a formula that does not use adsorbent. The effect of adsorbent on physical properties of matrix tablets was visually observed. It was found that colloidal silicon dioxide at the concentration of 5.0% by weight was the most suitable adsorbent for sodium valproate. Results are shown in Table 15.

Table 15 Adsorbent property of veegum and colloidal silicon dioxide

No absorbent	Veegum		colloidal silicon dioxide	
	2.5%w/w	5.0%w/w	2.5%w/w	5.0%w/w
exhibited sticking	exhibited sticking	exhibited sticking	exhibited sticking	non sticking

Colloidal silicon dioxide could be used as adsorbent for sodium valproate because it is a submicroscopic fumed silica with a particle size is about 15 nm. It is a light, loose, blueish-white coloured, odorless, tasteless, nongritty amorphous powder. While, veegum is a fine, micronized powder, off-white to creamy-white coloured, odorless, tasteless, soft, slippery small flakes. The powder varies from 45 to 297 μm in size. According to the physical properties and particle size, colloidal silicon dioxide exhibits larger surface area of the particles than veegum. As a result, colloidal silicon dioxide exhibited better adsorption than veegum.

Colloidal silicon dioxide has been used in several pharmaceutical applications; for example, adsorbent; anticaking agent; emulsion stabilizer; glidant; suspending agent; tablet disintegrant; thermal stabilizer; viscosity-increasing agent (Handbook of pharmaceutical excipient, 2009). Therefore, colloidal silicon dioxide was chosen for the next experiment.

3. **Effect of preparation method on drug release from sodium valproate matrix tablet**

Direct compression method

The formulation was composed of 230.0 mg of sodium valproate (equivalent to valproic acid 200 mg), 20.0 mg of ethylcellulose, 118 mg of dibasic calcium phosphate, 20.0 mg of colloidal silicon dioxide and 12.0 mg of talcum. The formulation exhibited

good flow and none sticking. The physical appearance of tablets were oblong shape, white in colour and smooth surface.

Wet granulation method

The formulation was composed of 230.0 mg of sodium valproate (equivalent to valproic acid 200 mg), 20.0 mg of ethylcellulose, 118 mg of dibasic calcium phosphate, 20.0 mg of colloidal silicon dioxide, 12.0 mg of talcum and 5%w/w PVP K90 in 95% ethyl alcohol. The formulation exhibited good flow and slightly sticking. The physical appearance of tablets were oblong shape, spotted and smooth surface.

The dissolution profile of sodium valproate matrix tablets prepared by direct compression and wet granulation methods are presented in Figure 9. The dissolution medium was deionized water. The obtained dissolution data were plot as percent cumulative drug release versus time.

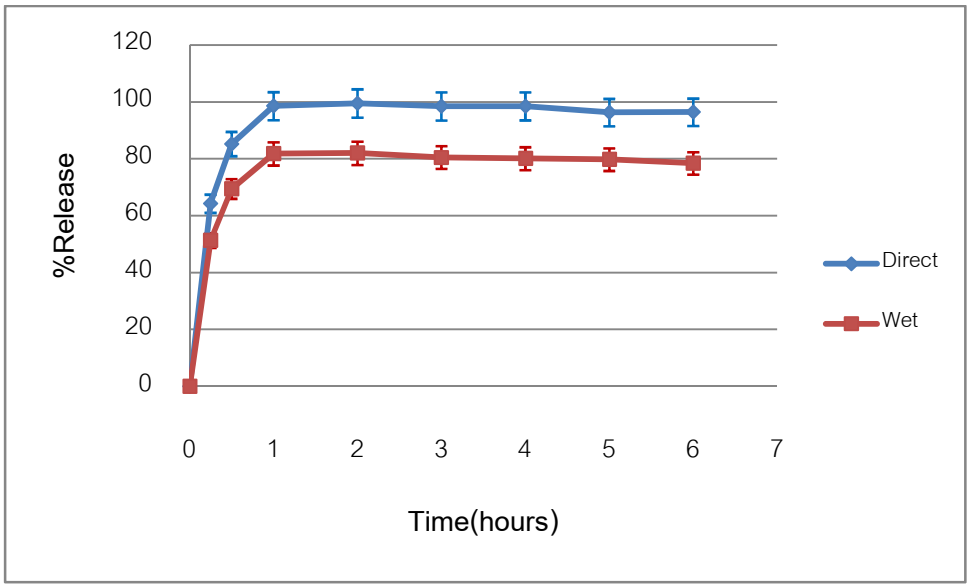


Figure 9 Effect of method on drug release from sodium valproate matrix tablet in deionized water

The dissolution profiles of sodium valproate matrix tablet prepared by direct compression method and wet granulation method were compared. A very rapid release of drug from all formulations was observed. All the formulations were released more than

70% of drug in first hour. The formulation prepared by direct compression method, released the drug about 96% in first hour. While, the formulation prepared by wet granulation method, released the drug about 78%. This may be due to initial burst effect caused by surface erosion or disaggregations of matrix tablets. As shown that the formulation prepared by direct compression method gave faster drug released than that prepared by wet granulation method.

Sodium valproate is highly hygroscopic nature, sodium valproate formulations often poses problem during production and storage. Therefore, the production process of sodium valproate tablet was required low humidity condition. However, wet granulation process had several steps and humidity in the production room was too high (40-50%RH). As a result, sodium valproate was lost in the process, especially sticking to the punches. Therefore, wet granulation method was not suitable for sodium valproate formulation. To enable production, usually high technical efforts have to be made and expensive equipment is necessary, such as air conditioning to low relative moisture. Because of wet granulation method not suitable for sodium valproate formulation, direct compression method was chosen for the next experiment.

4. **Effect of different polymers on drug release from sodium valproate matrix tablet by direct compression method**

All the formulations were composed of 230.0 mg of sodium valproate (equivalent to valproic acid 200 mg), 20.0 mg of colloidal silicon dioxide and 12.0 mg of talcum and required amount of dibasic calcium phosphate as diluent. The various polymers used were : ethylcellulose, HPMC E4M, HPMC K15M, xanthan gum, carrageenan, sodium alginate, Kollidon® SR, Eudragit® RSPO at the concentration of 5%, 10%. 15% and 20% by weight and the amount of dibasic calcium phosphate was decrease as the concentration of polymer was increased. All formulations exhibited good flow and none sticking because of colloidal silicon dioxide used as the adsorbent and diluents at the concentration of 5% by weight (below 5% exhibited sticking tablets). The physical appearance of tablets prepared with different types of polymer were oblong shape,

white in colour and smooth surface. The dissolution profiles of each formulation are presented in Figure 10-17. The dissolution medium was deionized water. The obtained dissolution data were plot as percent cumulative drug release versus time. A very rapid release of drug from all formulations was observed. All formulations released the drug more than 30% in the first hour. This may be due to initial burst effect caused by surface erosion or disaggregations of matrix tablets prior to gel layer formation around the tablet core (Kar, et al., 2009). Among the eight polymers used in the matrix tablets, ethylcellulose, HPMC E4M, carrageenan, sodium alginate, Kollidon® SR and Eudragit® RSPO were not proved to be a sustaining polymer for sodium valproate matrix tablets, As the concentration of ethylcellulose was increased from 5% to 20% by weight, the cumulative drug release whithin one hour were 96.40%, 96.60%, 87.43% and 82.43% as same as those of HPMC E4M were 87.91%, 95.65%, 96.71% and 90.66%, carrageenan were 84.05%, 81.76%, 81.46% and 84.05%, sodium alginate were 84.75%, 86.86%, 96.40% and 84.82%, Kollidon® SR were 93.29%, 84.30%, 82.82% and 84.61%, Eudragit® RSPO were 88.06%, 87.03%, 84.56% and 83.62%, respectively, except xanthan gum showing sustained action. The cumulative drug released from xanthan gum matrix tablets were 81.45%, 75.82%, 71.75% and 69.90%, respectively but high erosion was observed. HPMC K15M manifested sustained action, associated with an increased concentration (5% to 20% by weight), the cumulative drug release were 97.69%, 94.50%, 82.79% and 87.16%, respectively. In case of low concentration of HPMC K15M (5% by weight), the hydrated matrix would be highly porous with a low degree of tortuosity leading to low gel strength, rapid erosion and rapid diffusion of drug from the matrix. As the concentration of HPMC K15M was increased from 5% to 20% by weight, the drug release rate was gradually decreased. With a higher polymer concentration, the resultant gel layer would be more viscous and the tightness of the swollen hydrogel network was increased. Compared with the other polymers, HPMC K15M exhibited more retardation of drug release.

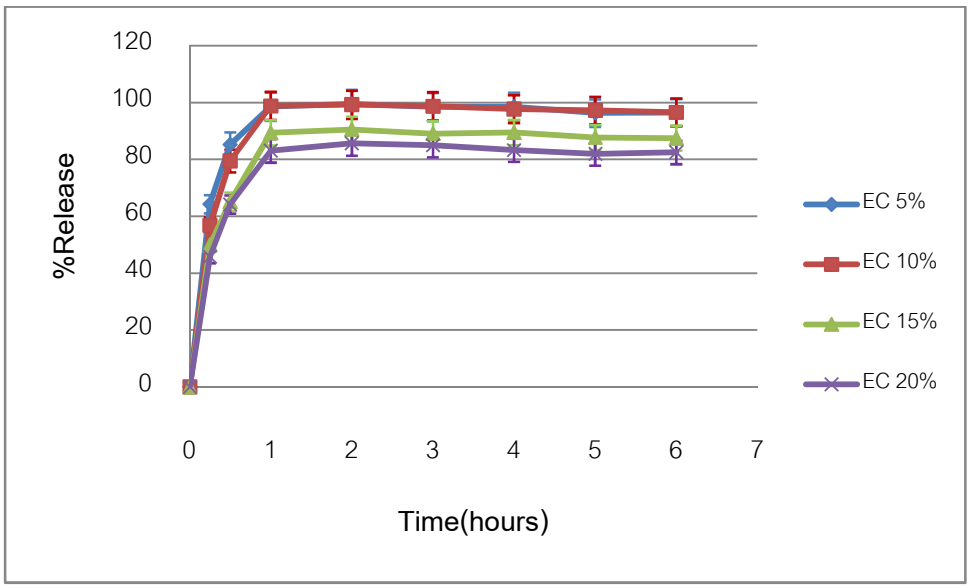


Figure 10 Effect of ethylcellulose on drug release from sodium valproate matrix tablet by direct compression method. Dissolution test was performed in 900 ml of deionized water.

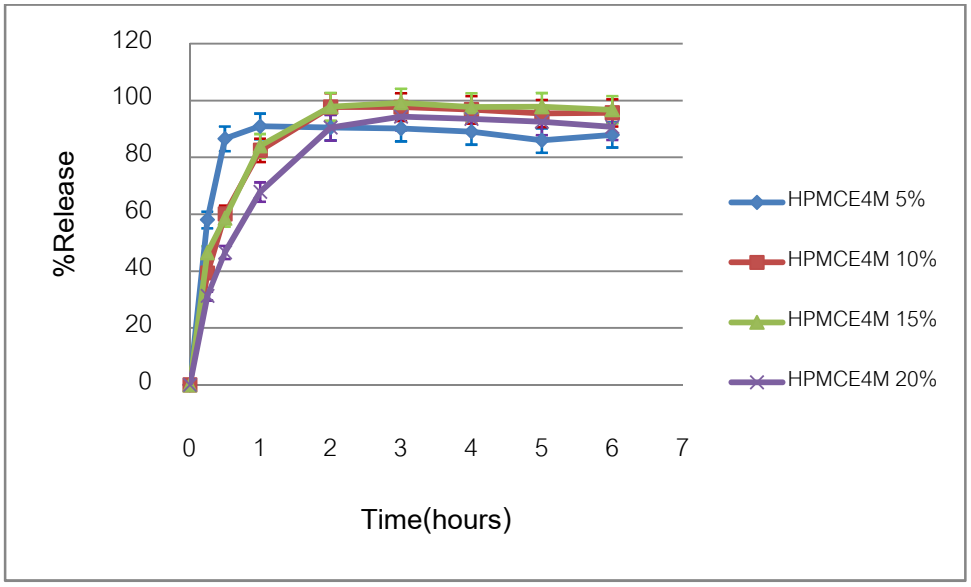


Figure 11 Effect of HPMC E4M on drug release from sodium valproate matrix tablet by direct compression method. Dissolution test was performed in 900 ml of deionized water.

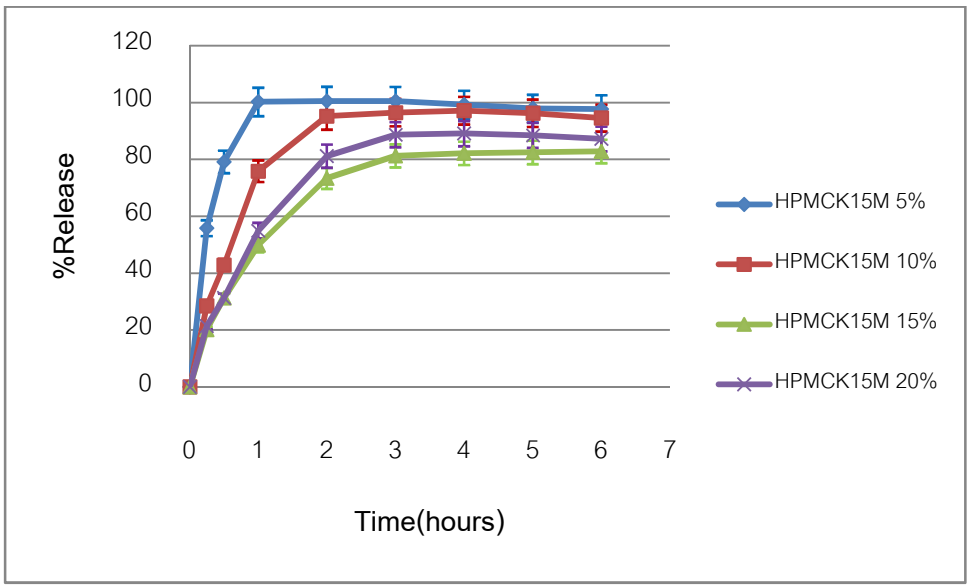


Figure 12 Effect of HPMC K15M on drug release from sodium valproate matrix tablet by direct compression method. Dissolution test was performed in 900 ml of deionized water.

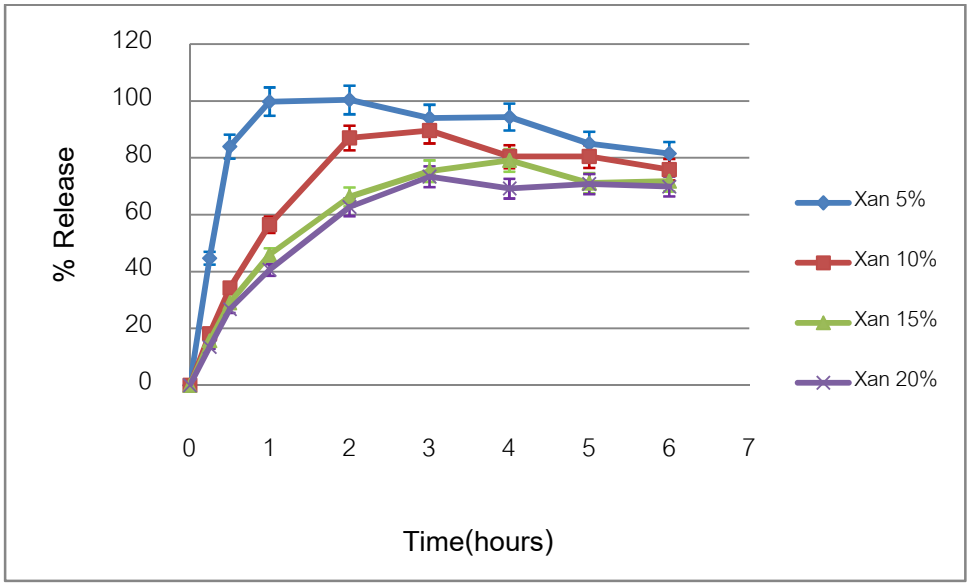


Figure 13 Effect of xanthan gum on drug release from sodium valproate matrix tablet by direct compression method. Dissolution test was performed in 900 ml of deionized water.

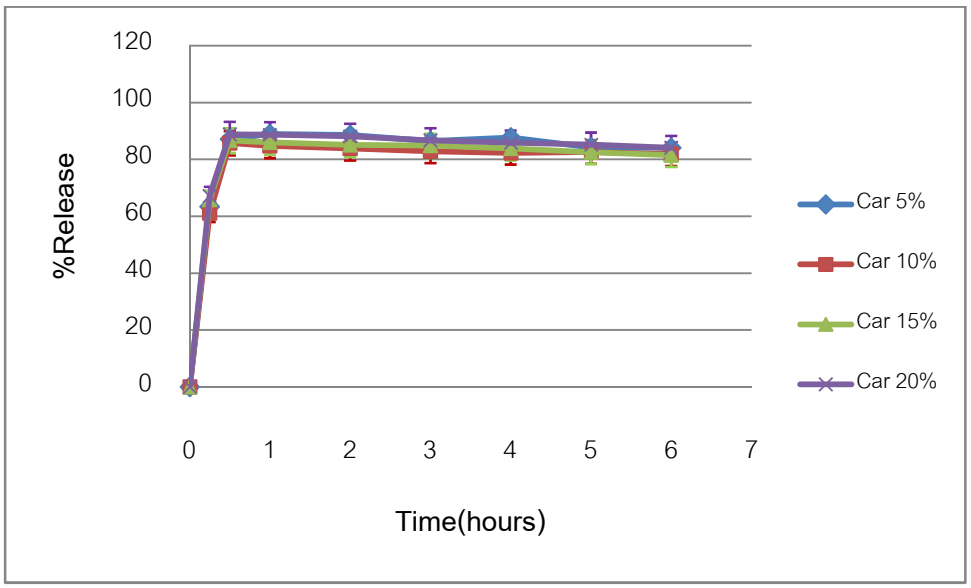


Figure 14 Effect of carrageenan on drug release from sodium valproate matrix tablet by direct compression method. Dissolution test was performed in 900 ml of deionized water.

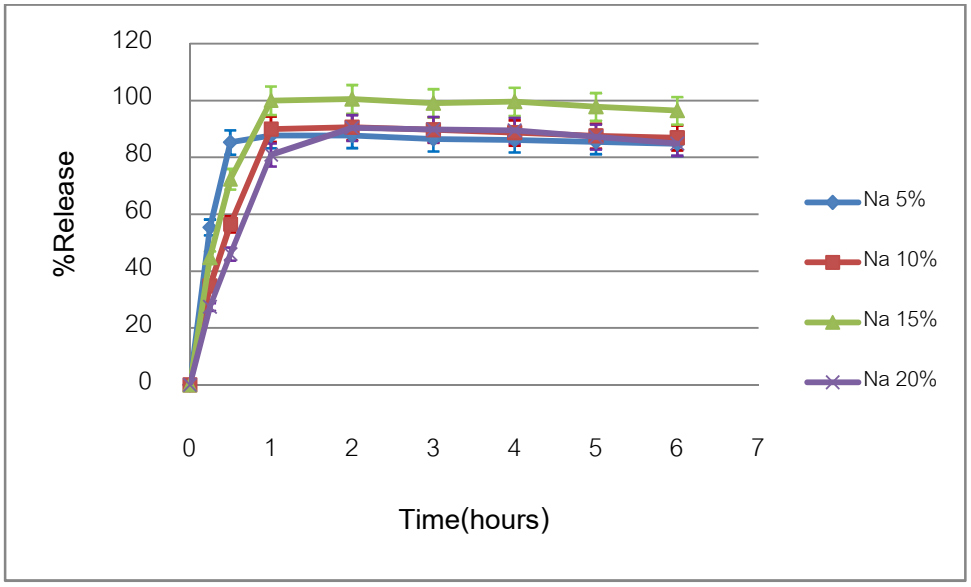


Figure 15 Effect of sodium alginate on drug release from sodium valproate matrix tablet by direct compression method. Dissolution test was performed in 900 ml of deionized water.

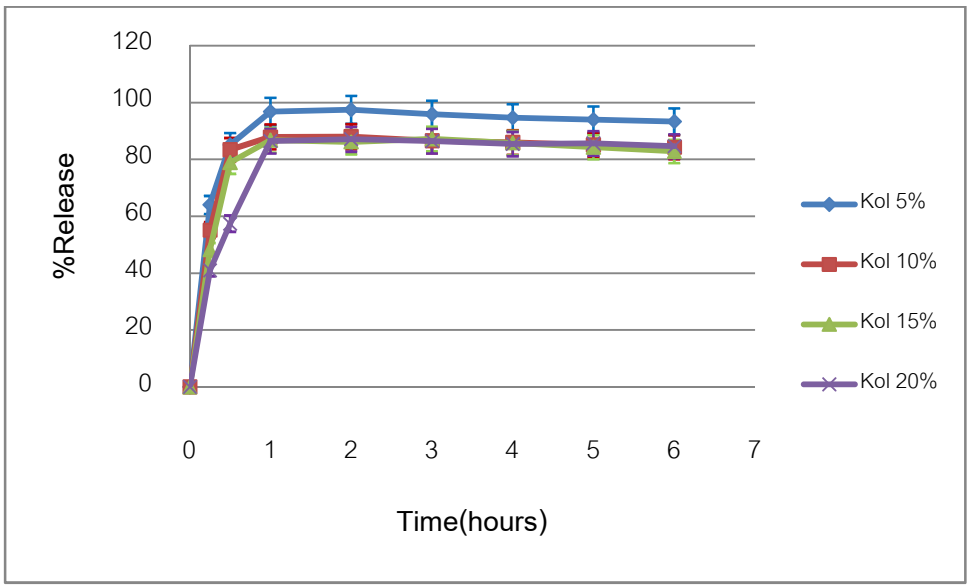


Figure 16 Effect of Kollidon® SR on drug release from sodium valproate matrix tablet by direct compression method. Dissolution test was performed in 900 ml of deionized water.

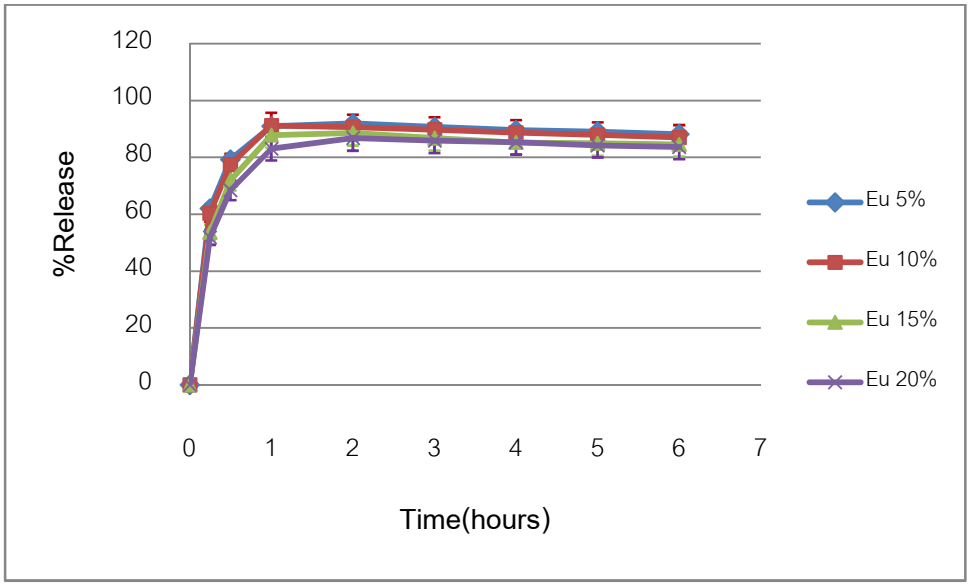


Figure 17 Effect of Eudragit® RSPO on drug release from sodium valproate matrix tablet by direct compression method. Dissolution test was performed in 900 ml of deionized water.

5. Preparation and evaluation of matrix tablets

5.1 Preparation of core matrix tablet

The formulation composed of 230.0 mg of sodium valproate (equivalent to valproic acid 200 mg), 20.0 mg of colloidal silicon dioxide, 12.0 mg of talcum, 118.0 mg of dibasic calcium phosphate and 20.0 mg of HPMC K15M following part 4 and select these formulation for the next experiment.

5.2 Design of bilayer tablet

Effect of different polymers used in the outer layer on drug release from sodium valproate matrix tablet

The formulation was composed of 200.0 mg of ethylcellulose and HPMC K15M as a first layer. The second layer composed of 230.0 mg of sodium valproate (equivalent to valproic acid 200 mg), 20.0 mg of colloidal silicon dioxide, 12.0 mg of talcum, 118.0 mg of dibasic calcium phosphate and 20.0 mg of HPMC K15M. All the formulations exhibited good flow and non sticking. The physical appearance of core matrix tablets were oblong shape, white in colour and smooth surface. While the physical appearance of bilayer tablet were oblong shape, two layer, white and yellowish white in colour and smooth surface. The dissolution profile of formulation is presented in Figure 19-20. The dissolution medium was deionized water. The obtained dissolution data were plot as percent cumulative drug release versus time. Comparison dissolution profiles between core matrix tablets and bilayer tablets, bilayer tablet gave more prolonged release than core matrix tablets.

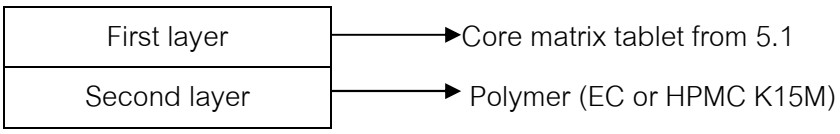


Figure 18 An oral sustained-release bilayer tablet, consisting of a first layer containing a pharmaceutical active ingredient, second layer containing polymer.

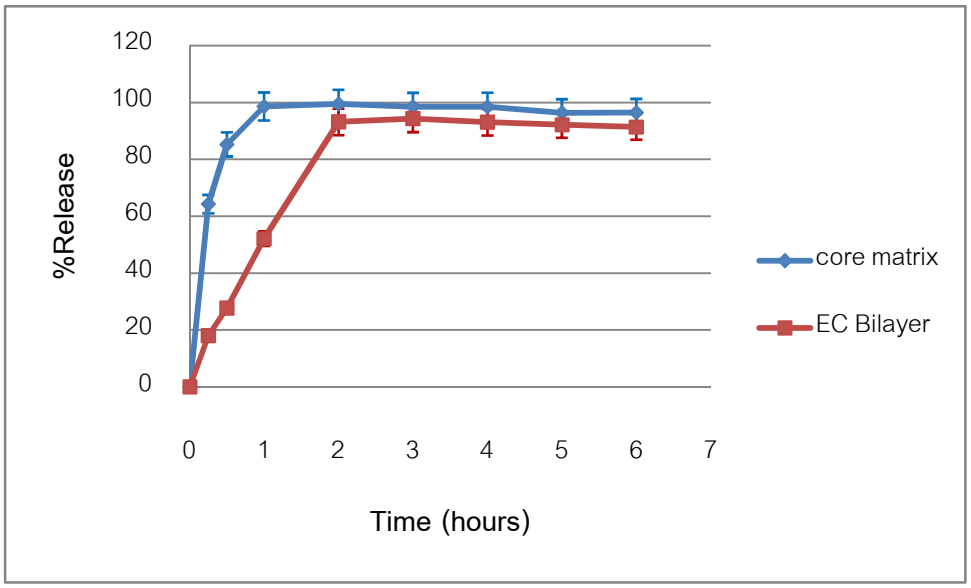


Figure 19 Effect of ethylcellulose used in the outer layer on drug release from sodium valproate matrix tablet. Dissolution test was performed in 900 ml of deionized water.

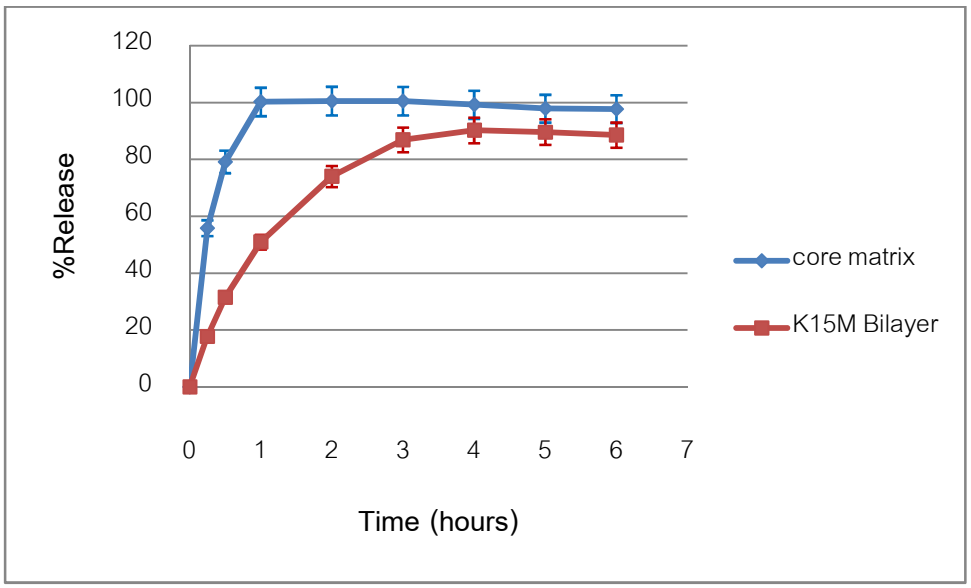


Figure 20 Effect of HPMC K15M used in the outer layer on drug release from sodium valproate matrix tablet. Dissolution test was performed in 900 ml of deionized water.

Comparison dissolution profiles between bilayer tablets were composed of ethylcellulose as the outer layer and bilayer tablets that composed of HPMC K15M as the outer layer. The drug release from bilayer tablets composed of ethylcellulose were faster than that of bilayer tablets composed of HPMC K15M (at 15-720 minutes), the cumulative drug release witin 24 hours was 85.79% and 83.99%, respectively. The outer layers composed of HPMC K15M, the release could follow by three steps. First step was the penetration of the dissolution medium in the bilyer tablet (hydration). Second step was the swelling which forms the gel layer with concomitant or subsequent diffusion and erosion of the bilayer tablet and third step the dissolving of the drug. The outer layers provide an excellent protection of the core tablet for extended times. This type of layer, being quite impermeable to drug diffusion for long periods of time, is particularly useful to control the release of sodium valproate. In case of ethylcellulose, it lack of the swellable property, so gel layer formation was to low to promote a rapid erosion and diffusion of drug from bilayer tablet. Therefore, bilayer tablets composed of HPMC K15M exhibied more prolonged release than bilayer tablets

composed of ethylcellulose. As shown in Figure 21. Conte et al, 1996 reported that the swellable layer that shown a stronger protective effect was more suitable to control the release of soluble drugs such as sodium valproate while the erodible layer provided a more accurate modulation of the dissolution profile of sparingly soluble drugs.

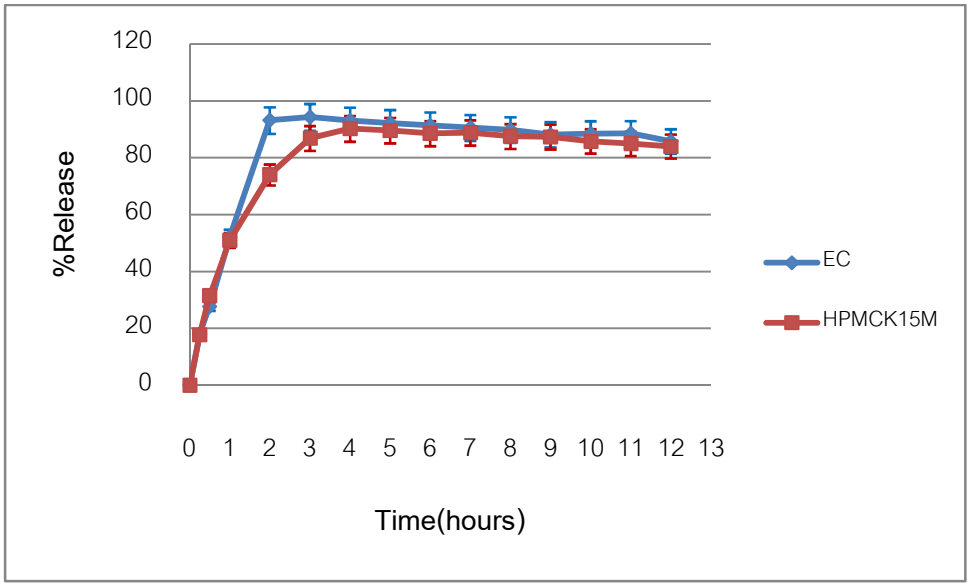


Figure 21 Effect of different polymers used in the outer layer on drug release from sodium valproate matrix tablet. Dissolution test was performed in 900 ml of deionized water.

Bilayer sustained release tablet composed of sodium valproate, dibasic calcium phosphate, colloidal silicon dioxide, talcum and HPMC K15M. While fixing the amount of colloidal silicon dioxide at the suitable minimum concentration at 5% by weight, the formulation overcame problems associated with highly hygroscopic drug like sodium valproate. HPMC K15M as the outer layer was successfully prepared to achieve slow release of sodium valproate, a highly water-soluble drug. HPMC K15M also imparted a more controlled influence on the release pattern of sodium valproate with reduction and/or elimination of the tendency of burst release which was evident in formulation. However, furture development is required to obtain more prolonged release of

sodium valproate from the system, i.e., application of trilayer and/or multilayer tablet technique.

5.3 Design of mutilayer sustained release tablets of sodium valproate

Mutilayer sustained release tablets of sodium valproate formulation exhibited good flow and none sticking. The physical appearance of mutilayer sustained release tablets of sodium valproate were oblong shape, three layer (trilayer), white inner layer and yellowish white outer layers and smooth surface (Figure 23).

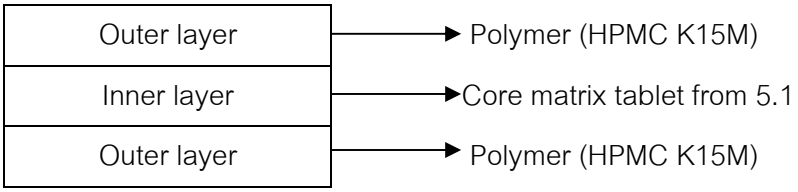


Figure 22 An oral sustained-release trilayer tablet, consisting of an inner layer containing a pharmaceutical active ingredient, outer layer containing polymer.

Top Bottom Lateral side

Figure 23 The physical appearance of mutilayer sustained release tablets of sodium valproate

6. Physical properties of mutilayer sustained release tablets of sodium valproate

The evaluation data composed of weight, thickness, hardness and friability. The data were presented in table 16.

Table 16 Evaluation data of mutilayer sustained release tablets of sodium valproate

Weight (mg.) ± S.D. (n = 20)	Thickness (mm.) ± S.D. (n = 10)	Hardness (Kp.) ± S.D. (n = 10)	Friability (%) (n = 10)
802.93 ± 3.02	4.51 ± 0.14	> 20	0.098

7. Dissolution studies of mutilayer sustained release tablets of sodium valproate

For the dissolution study of mutilayer sustained release tablets of sodium valproate was determined by using USP apparatus I (basket) dissolution tester, operating at 100 rpm. Dissolution test was performed in 900 ml of deionized water for 24 hours, 0.1 N HCl for 24 hours, 6.8 pH phosphate buffer for 24 hours and pH change (0.1 N HCl for 2 hours followed by 6.8 pH phosphate buffer until 24 hours), The dissolution profile of formulation is presented in Figure 24. The obtained dissolution data were plot as percent cumulative drug release versus time.

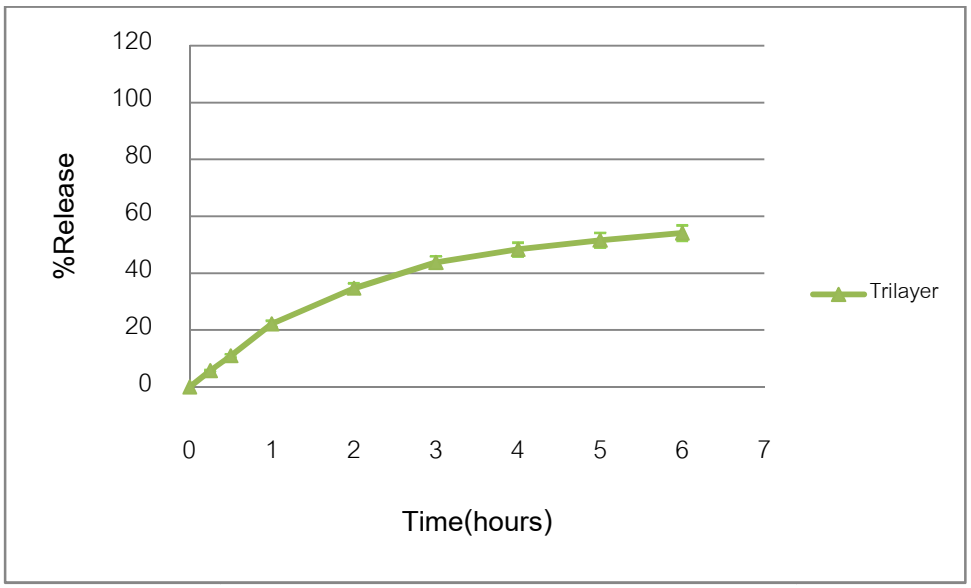


Figure 24 Dissolution profile of mutilayer sustained release tablets of sodium valproate in deionize water

An oral multilayer sustained release tablet, more particularly, a multilayer tablet consisting of an inner layer containing a pharmaceutically active ingredient and two outer layers containing swelling polymers. On expose to dissolution medium, the two outer layers swell to form gelled layers surrounding the lateral side of the inner layer rapidly (Figure 25), thereby control effectively the releases of drug from the inner immediate-release layer (Park et al., 2010).

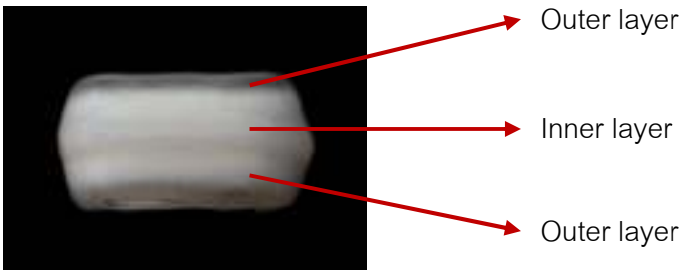


Figure 25 Multilayer sustained release tablet of sodium valproate on expose to dissolution medium at 6 hours

In this study, HPMC K15M was used as a swellable polymer. After trilayer tablet exposed to dissolution medium, sodium valproate which was water soluble drug deposited on lateral side of the inner layer could dissolve and two outer layers swell to form gelled layers surrounding the lateral side of the inner layer. Therefore, the drug could gradually diffuse out from trilayer tablet. This property is lead to the retardation of drug release.

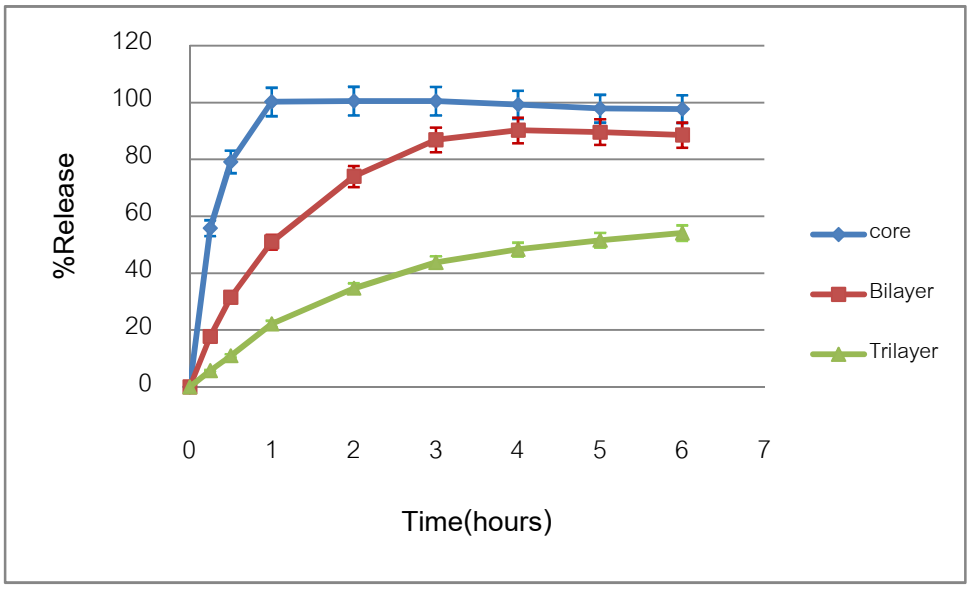


Figure 26 Comparison dissolution profiles between core matrix tablets, bilayer tablets and mutilayer sustained release tablets of sodium valproate (trilayer) in deionized water

Figure 26 showed a comparison dissolution profiles for 6 hours between core matrix tablets, bilayer tablets and trilayer tablet. While, the layer was increased from 1 layer to 3 layers, the drug release rate was gradually decreased. Therefore, selection trilayer tablet for dissolution study for 24 hours in various dissolution medium. As shown in Figure 28.

Multilayer sustained release tablets of sodium valproate

Initial After 6 hours After 24 hours

Figure 27 The physical appearance of multilayer sustained release tablets of sodium valproate after exposed to dissolution medium (deionized water) at 0, 6 and 24 hours

Multilayer sustained release tablets of sodium valproate consisting of an inner layer containing a sodium valproate and two outer layers containing HPMC K15M. On expose to dissolution medium, the two outer layers swell to form gelled layers surrounding the lateral side of the inner layer rapidly. As shown in Figure 27.

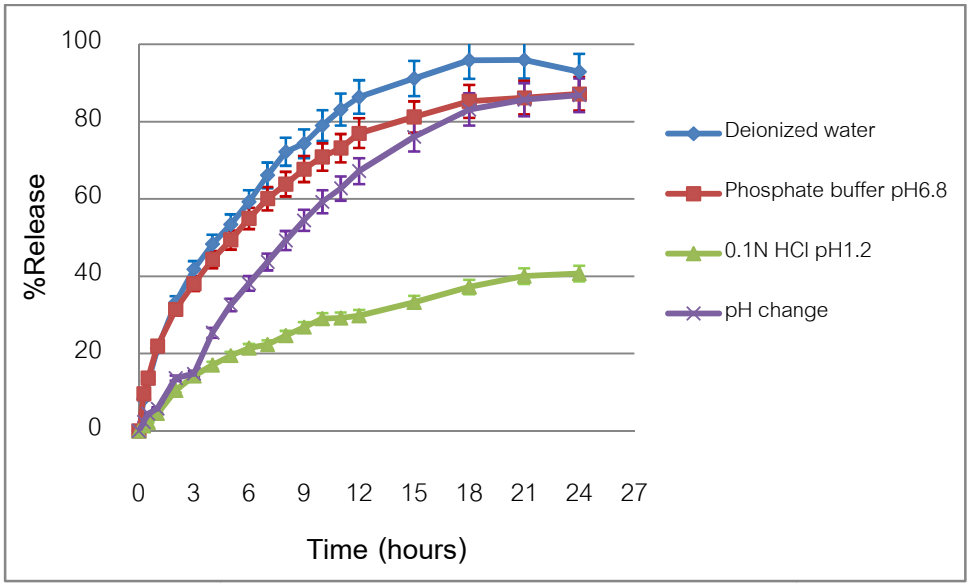


Figure 28 Dissolution profile of multilayer sustained release tablets of sodium valproate in various dissolution medium such as deionized water, 0.1 N HCl pH 1.2, phosphate buffer pH 6.8 and pH change (0.1 N HCl pH 1.2 followed by phosphate buffer pH 6.8)

Figure 28, as the pH of dissolution medium was increased, the drug release rate was obviously increased. pH of dissolution medium had appreciable effect on drug release profile which was in the rank order of 88.92% at 24 hours in deionized water, 91.76% at 24 hours in phosphate buffer pH 6.8, 84.53% at 24 hours in pH change (0.1 N HCl pH 1.2 followed by phosphate buffer pH 6.8) and 41.87% at 24 hours in 0.1 N HCl pH 1.2, respectively. Sodium valproate is synthetic origin and belongs to valproic acid. It has a high degree of ionization and belongs to Na-channel antagonist pharmacological group on the basis of mechanism of action. Its pKa is 4.95. The ionized form of the drug (salt of the weak acid) will have greater solubility in dissolution medium that contained polar solvents (water) which readily dissolve polar solutes such as salts (ionic compounds) than the unionized weak acid or weak base (Thompson, 2004). Result also indicate that in deionized water, phosphate buffer pH 6.8 and pH change, the amount of drug release is more than 0.1 N HCl pH 1.2.

8. **Design of mutilayer sustained release tablets of sodium valproate combined with valproic acid**

Multilayer sustained release tablets of sodium valproate combined with valproic acid formulation exhibited good flow and do not stick to punch and dies. The physical appearance of multilayer tablet were oblong shape, three layers (trilayer), white inner layer and yellowish white outer layer in colour and smooth surface as same as multilayer sustained release tablets of sodium valproate (Figure 30).

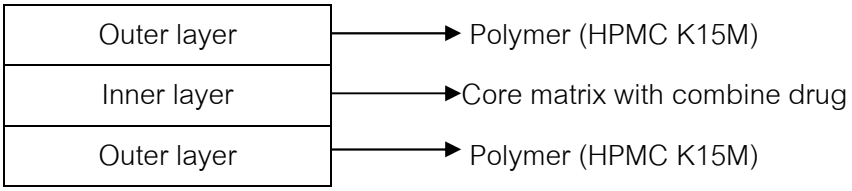


Figure 29 An oral sustained-release trilayer tablet, consisting of an inner layer containing a pharmaceutical active ingredient (sodium valproated combined with valproic acid), outer layer containing polymer.

Top Bottom Lateral side

Figure 30 The physical appearance of mutilayer sustained release tablets of sodium valproate combined with valproic acid

9. **Physical properties of mutilayer sustained release tablets of sodium valproate combined with valproic acid**

The evaluation data composed of weight, thickness, hardness and friability. The data were presented in table 17.

Table 17 Evaluation data of mutilayer sustained release tablets of sodium valproate combined with valproic acid

Weight (mg.) ± S.D. (n = 20)	Thickness (mm.) ± S.D. (n = 10)	Hardness (Kp.) ± S.D. (n = 10)	Friability (%) (n = 10)
804.14 ± 3.07	4.57 ± 0.12	> 20	0.098

10. **Dissolution studies of mutilayer sustained release tablets of sodium valproate combined with valproic acid**

Follow by dissolution studies of mutilayer sustained release tablets of sodium valproate. An oral multilayer sustained release tablets of sodium valproate combined with valproic acid, more particularly, a multilayer tablet consisting of an inner layer containing two pharmaceutically active ingredients (sodium valproate and valproic acid) and two outer layers containing swelling polymers. On expose to dissolution medium, the two outer layers swell to form gelled layers surrounding the lateral side of the inner layer rapidly as same as multilayer sustained release tablets of sodium valproate,

thereby effectively control the releases of drug from the inner immediate-release layer (Park et al., 2010).

In this study, HPMC K15M was used as a swellable polymer. After multilayer tablet exposed to various dissolution medium such as deionized water, 0.1 N HCl pH 1.2, phosphate buffer pH 6.8 and pH change (0.1 N HCl pH 1.2 followed by phosphate buffer pH 6.8), sodium valproate which was water soluble drug deposited on lateral side of the inner layer could dissolve while valproic acid was slightly soluble in water (1.3 mg/mL) thus it could dissolve slowly, and two outer layers swell to form gelled layers surrounding the lateral side of the inner layer. Therefore, the drugs could gradually diffuse out from multilayer tablet. This property is lead to the retardation of drug release.

Multilayer sustained release tablets of sodium valproate combined with valproic acid

Initial After 6 hours After 24 hours

Figure 31 The physical appearance of multilayer sustained release tablets of sodium valproate combined with valproic acid after exposed to dissolution medium at 0, 6 and 24 hours

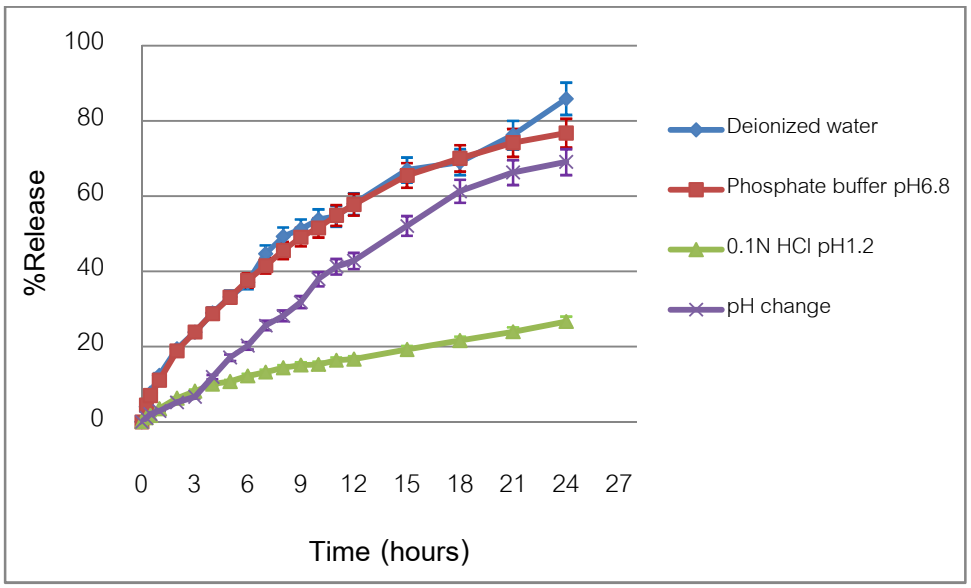


Figure 32 Dissolution profile of multilayer sustained release tablets of sodium valproate combined with valproic acid in various dissolution medium such as deionized water, 0.1 N HCl pH 1.2, phosphate buffer pH 6.8 and pH change (0.1 N HCl pH 1.2 followed by phosphate buffer pH 6.8)

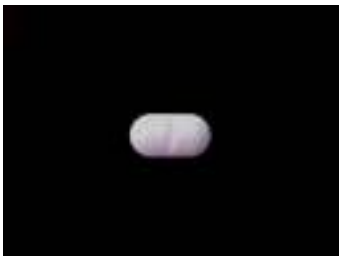
As shown in Figure 32, the pH of dissolution medium were increased, the drug release rate was obviously increased. pH of dissolution medium had appreciable effect on drug release profile which was in the rank order of 85.87% at 24 hours in deionized water, 76.72% at 24 hours in phosphate buffer pH 6.8, 69.03% at 24 hours in pH change (0.1 N HCl pH 1.2 followed by phosphate buffer pH 6.8) and 26.64% at 24 hours in 0.1 N HCl pH 1.2, respectively. Sodium valproate will have greater solubility in dissoluion medium than valproic acid while, valproic acid has a high degree of ionization at pH 7.4. Its pKa is 4.80, that are relatively insoluble or slightly soluble in water (1.3 mg/ml) may exhibit poor dissolution characteristics. The release profiles of multilayer sustained release tablets of sodium valproate combined with valproic were different from multilayer sustained release tablets of sodium valproate. As shown that multilayer sustained release tablets of sodium valproate formulation could release drug from tablet faster than multilayer sustained release tablets of sodium valproate combined with valproic

11. **Comparison dissolution profile between multilayer sustained release tablets of sodium valproate, multilayer sustained release tablets of sodium valproate combined with valproic acid, Depakine chrono® and Encorate chrono®**

Dissolution profiles of multilayer sustained release tablets of sodium valproate compared to multilayer sustained release tablets of sodium valproate combined with valproic acid and a commercial product, Depakine Chrono® 500 mg and Encorate Chrono® 200 mg. Dissolution test was performed in 900 ml of 0.1 N HCl for 24 hours, 6.8 pH phosphate buffer and pH change (0.1 N HCl for 2 hours followed by 900 ml of 6.8 pH phosphate buffer), as shown in Figure 35-37. The physical appearance of Depakine chrono® and Encorate chrono® after exposed to dissolution medium at 0, 6 and 24 hours as shown in Figure 33-34.

Depakine chrono®

Top



Initial

After 6 hours

After 24 hours

Initial

After 6 hours

After 24 hours

Lateral side

Initial After 6 hours After 24 hours

Figure 33 The physical appearance of Depakine chrono® after exposed to dissolution medium (6.8 pH phosphate buffer) at 0, 6 and 24 hour

Encorate chrono®

Top

Initial After 6 hours After 24 hours

Initial After 6 hours After 24 hours

Lateral side

Initial After 6 hours After 24 hour

Figure 34 The physical appearance of Encorate chrono® after exposed to dissolution medium (6.8 pH phosphate buffer) at 0, 6 and 24 hours

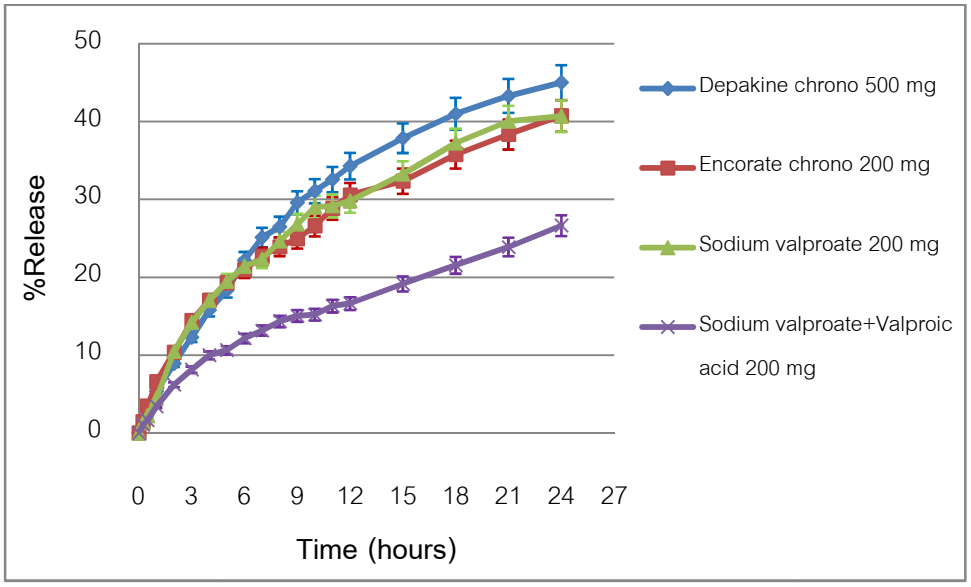


Figure 35 Comparison dissolution profile between multilayer sustained release tablets of sodium valproate, multilayer sustained release tablets of sodium valproate combined with valproic acid, Depakine chrono® and Encorate chrono® in 0.1 N HCl

Figure 35, comparison dissolution profiles between multilayer sustained release tablets of sodium valproate, multilayer sustained release tablets of sodium valproate combined with valproic acid, Depakine chrono® and Encorate chrono® in 0.1 N HCl, the drug release rate was 40.70%, 26.64%, 44.99% and 40.73%, respectively.

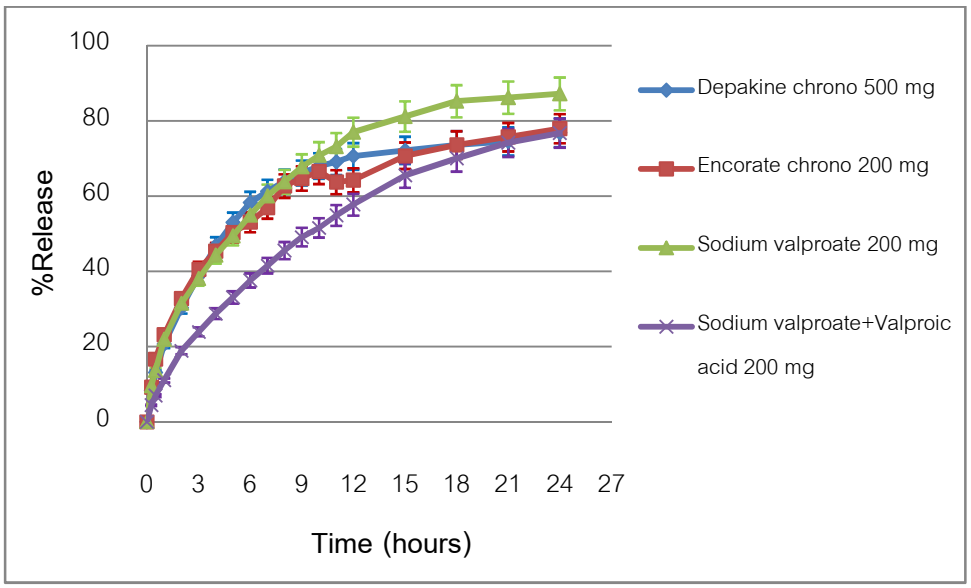


Figure 36 Comparison dissolution profile between multilayer sustained release tablets of sodium valproate, multilayer sustained release tablets of sodium valproate combined with valproic acid, Depakine chrono® and Encorate chrono® in 6.8 pH phosphate buffer

Figure 36, comparison dissolution profiles between multilayer sustained release tablets of sodium valproate, multilayer sustained release tablets of sodium valproate combined with valproic acid, Depakine chrono® and Encorate chrono® in 6.8 pH phosphate buffer, the drug release rate was 87.17%, 76.72%, 76.83% and 77.91%, respectively.

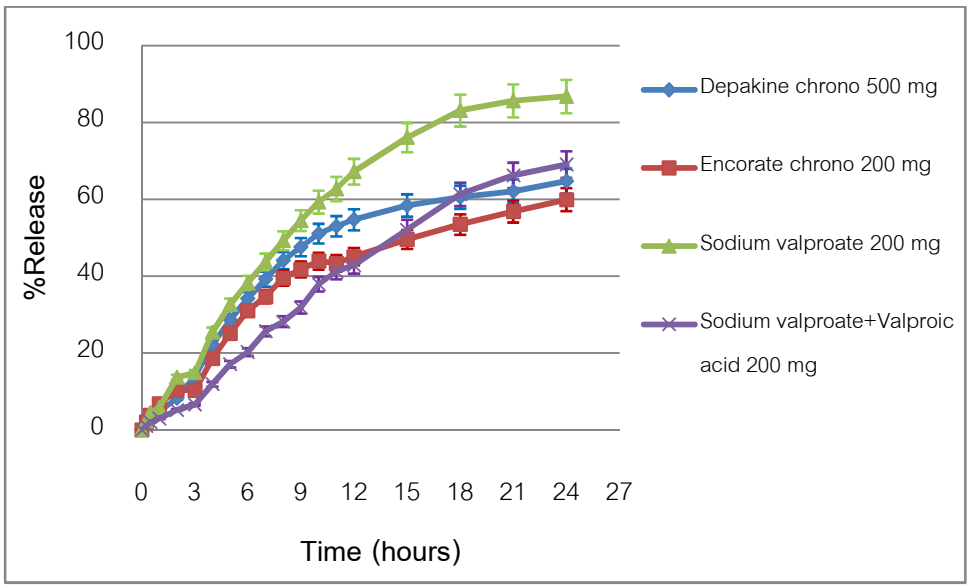


Figure 37 Comparison dissolution profile between multilayer sustained release tablets of sodium valproate, multilayer sustained release tablets of sodium valproate combined with valproic acid, Depakine chrono® and Encorate chrono® in pH change (0.1 N HCl for 2 hours followed by 900 ml of 6.8 pH phosphate buffer)

Figure 37, comparison dissolution profiles between multilayer sustained release Tablets of sodium valproate, multilayer sustained release tablets of sodium valproate combined with valproic acid, Depakine chrono® and Encorate chrono® in pH change (0.1 N HCl for 2 hours followed by 900 ml of 6.8 pH phosphate buffer), the drug release rate was 86.77%, 69.03%, 64.72% and 59.89%, respectively.

In case of Depakine chrono® and Encorate chrono® were prepared as matrix system, which release the drug in continuous manner. These release the drug by both dissolution controlled as well as diffusion controlled mechanisms. To control the release of the drugs, which are having different solubility properties, the drug is dispersed in swellable hydrophilic polymer. While multilayer sustained release tablets, it consists of a hydrophilic matrix core, containing the active ingredient, and two swellable hydrophilic polymers applied on outer layers of the core (Conte et al., 1996). The presence of the hydration and swelling rate of the core and reduces the surface area available for drug

release. Multilayer sustained release tablets of sodium valproate contained only sodium valproate. Its different from other formulation that contained combined drug, sodium valproate and valproic acid. Since sodium valproate is a water soluble drug, therefore, when dissolution medium penetrated to multilayer tablet, sodium valproate deposited on lateral side of the inner layer could rapidly dissolve and diffuse out through gel layer to dissolution medium. While, the formulation contained combined drug, valproic acid was slightly soluble in water (1.3 mg/mL) thus the release rates obtained are generally too slow, it could dissolve in dissolution medium less than sodium valproate. As a result, multilayer sustained release tablets of sodium valproate formulation could release drug from tablet faster than other formulation that contained a combined drug, sodium valproate and valproic acid.

12. **Kinetic analysis of dissolution profiles of multilayer sustained release tablets of sodium valproate, multilayer sustained release tablets of sodium valproate combined with valproic acid, Depakine chrono® and Encorate chrono®**

The kinetic analysis of dissolution profiles has been attempted using different release models. Drug Release data were fitted to kinetic model including the zero-order (cumulative amount of drug release versus time), first-order (log cumulative % of drug remaining versus time), Higuchi (cumulative % of release versus square root of time) and Korsmeyer-Peppas(log cumulative % drug release verses log time). As shown in Figure 38-41.

Table 18 The kinetic analysis of dissolution profiles

Formulation	R^2			
	Zero order	First order	Higuchi	Korsmeyer-Pepas
Multilayer sustained release tablets of sodium valproate	0.993	0.991	0.949	0.948
Multilayer sustained release tablets of sodium valproate combined with valproic acid	0.991	0.981	0.902	0.853
Depakine chrono®	0.982	0.992	0.950	0.912
Encorate chrono®	0.964	0.970	0.948	0.940

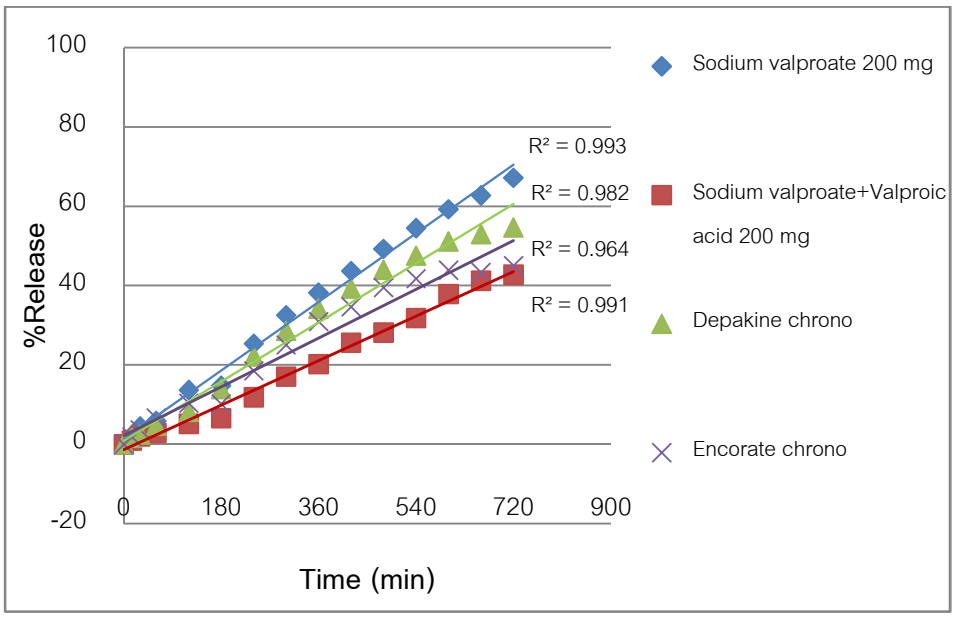


Figure 38 Zero order release model of multilayer sustained release tablets of sodium valproate, multilayer sustained release tablets of sodium valproate combined with valproic acid, Depakine chrono® and Encorate chrono®

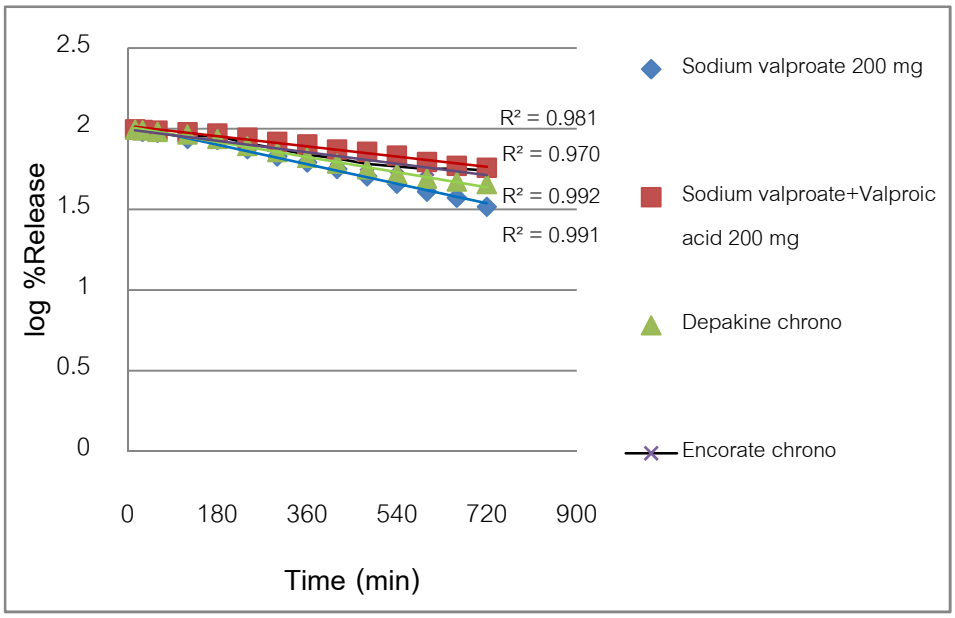


Figure 39 First order release model of multilayer sustained release tablets of sodium valproate, multilayer sustained release tablets of sodium valproate combined with valproic acid, Depakine chrono® and Encorate chrono®

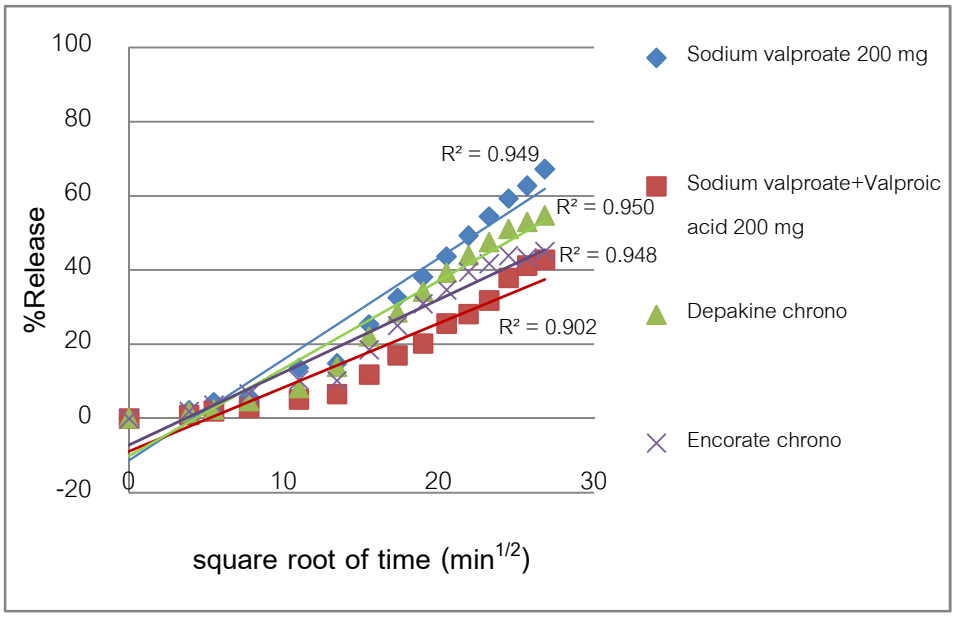


Figure 40 Higuchi release model of multilayer sustained release tablets of sodium valproate, multilayer sustained release tablets of sodium valproate combined with valproic acid, Depakine chrono® and Encorate chrono®

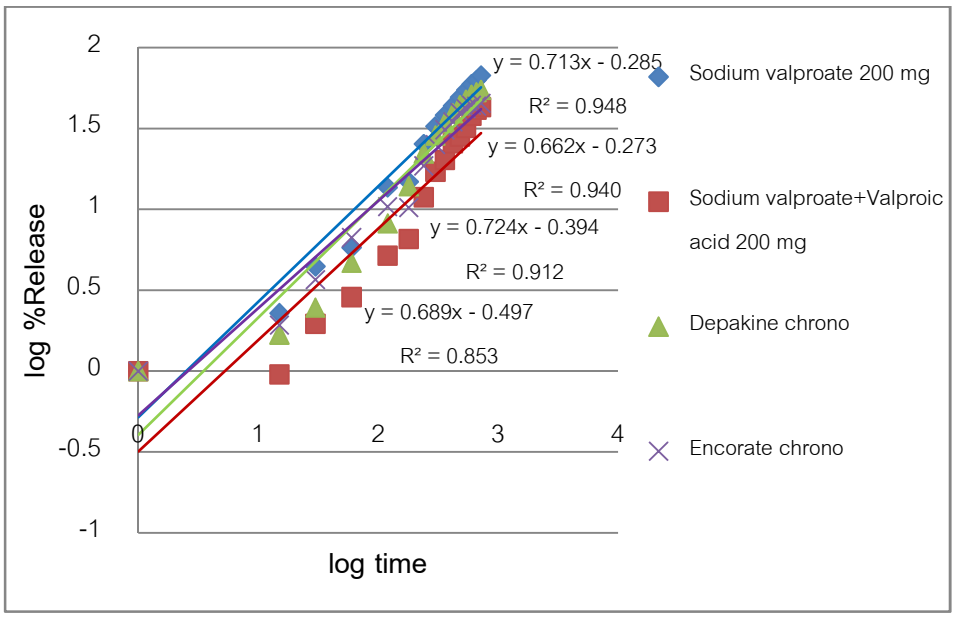


Figure 41 Korsmeyer-Peppas release model of multilayer sustained release tablets of sodium valproate, multilayer sustained release tablets of sodium valproate combined with valproic acid, Depakine chrono® and Encorate chrono®

Multilayer sustained release tablets of sodium valproate, multilayer sustained release tablets of sodium valproate combined with valproic acid, Depakine chrono® and Encorate chrono® were determined by fitting drug release data to kinetic model including the zero-order, first-order, Higuchi and Korsmeyer-Peppas. The co-efficient of determination (R^2) was used as an indicator of the best fitting for each of the models considered. In case of multilayer sustained release tablets of sodium valproate and multilayer sustained release tablets of sodium valproate combined with valproic acid, drug release kinetics shown that drug release was best explained by zero order release model, which often used to describe the drug dissolution of several types of modified release pharmaceutical dosage forms, as in case of some transdermal systems, as well as matrix tablets with low soluble drugs in coated forms, osmotic systems, etc (Freitas, 2005). Zero order plots showed the highest linearity (R^2 = 0.993) for multilayer sustained release tablets of sodium valproate and (R^2 = 0.991) for multilayer sustained release tablets of sodium valproate combined with valproic acid, followed by first order kinetic

model (R^2 = 0.991 and 0.981) and Higuchi kinetic model (R^2 = 0.949 and 0.902). However, in case of multilayer sustained release tablets of sodium valproate, R^2 from zero order was similar to first order (R^2 = 0.993 and 0.991) as shown that could not differentiate between zero order and first order. While, In case of Depakine chrono® and Encorate chrono®, drug release kinetics shown that drug release was best explained by first order release model, which often used to describe the drug dissolution in pharmaceutical dosage forms such as those containing water-soluble drugs in porous matrices. First order plots showed the highest linearity (R^2 = 0.992) for Depakine chrono® and (R^2 = 0.970) for Encorate chrono® followed by zero order kinetic model (R^2 = 0.982 and 0.964) and Higuchi kinetic model (R^2 = 0.950 and 0.948). Korsmeyer–Peppas model is available in different shapes; slap, cylinder and sphere but release exponent values (n) are slightly different. Korsmeyer's plots indicated an n value of 0.713, 0.689, 0.724 and 0.662, respectively which was indicative of non-fickian diffusion, ananomalous diffusion mechanism or diffusion coupled with erosion. Therefore, the drug release was controlled by multiple mechanisms.

CHAPTER V
CONCLUSIONS

In conclusion, the analytical HPLC method was developed and validated carefully for determination an amount of sodium valproate and valproic acid. The developed method was simple and responsive which could be employed for quantity analysis of formulation.

Sodium valproate matrix tablet were prepared by direct compression method that composed of dibasic calcium phosphate, talcum and HPMC K15M. Colloidal silicon dioxide could effectively adsorb sodium valproate. The formulation overcame problems associated with highly hygroscopic drug like sodium valproate. Matrix of HPMC K15M as the gelation polymer was successfully prepared to achieve slow release of sodium valproate. HPMC K15M also imparted a more controlled influence on the release pattern of sodium valproate.

Comparison dissolution profiles between core matrix tablets, bilayer tablets and trilayer tablet. While, the layer was increased from 1 layer to 3 layers, the drug release rate was gradually decreased. HPMC K15M as the outer layer could effectively to control release of sodium valproate. Dissolution profile of multilayer sustained release tablets of sodium valproate, as the pH of dissolution medium were increased, the drug release rate was obviously increased similar to the multilayer sustained release tablets of sodium valproate combined with valproic acid.

Different dissolution models were applied to the drug release data in order to evaluate release mechanism and kinetics. In case of multilayer sustained release tablets of sodium valproate and multilayer sustained release tablets of sodium valproate combined with valproic acid, drug release kinetics shown that drug release was best explained by zero order release model while, in case of Depakine chrono® and Encorate chrono®, drug release kinetics shown that drug release was best explained by first order

release model. Korsmeyer's plots indicated an n value of 0.713, 0.689, 0.724 and 0.662, respectively which was indicative of non-fickian diffusion.

Comparison dissolution profiles between multilayer sustained release tablets of sodium valproate, multilayer sustained release tablets of sodium valproate combined with valproic acid and a commercial product, Depakine chrono® and Encorate chrono®. Multilayer sustained release tablets of sodium valproate formulation could release drug from tablet faster than other formulation that contained a combined drug, sodium valproate and valproic acid.

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APPENDICES

APPENDIX A

HPLC VALIDATION

1. Linearity

Conc. (mg/ml)	Peak area					
	n 1	n 2	n 3	mean	SD	%RSD
0.2	139045	139998	140102	139715	582.56	0.42
0.4	281835	281625	279823	281094.3	1106.00	0.39
0.6	418429	415951	419158	417846	1681.11	0.40
0.8	564781	566104	564421	565102	886.23	0.16
1.0	703317	703187	692415	699639.7	6257.08	0.89

2. Accuracy

Level (%)	Peak area					
	n 1	n 2	n 3	mean	SD	%RSD
50	1025823	1019441	1023190	1022818	2618.69	0.26
100	1988520	1996108	1984721	1989783	4733.73	0.24
150	2984147	2969731	2991445	2981774	9022.07	0.30

3. Precision

n	Intra-day	Inter-day
1	703317	702814
2	703187	701926
3	696341	702070
4	699987	702805
5	704459	702167
6	698375	702279
Mean	700944.3	702279
SD	3216.29	434.68
%RSD	0.46	0.06

4. Sample solution stability

Day	Peak area					
	n 1	n 2	n 3	mean	SD	%RSD
Day-1	692984	696074	696341	695133	1523.48	0.22
Day-5	694591	698606	695775	696324	1684.46	0.24

APPENDIX B

DRUG RELEASE DATA

1. Effect of preparation method on drug release from sodium valproate matrix tablet

Direct compression method

Time (min)	%Release				
	n 1	n 2	n 3	mean	SD
0	0.00	0.00	0.00	0.00	0.00
15	55.23	64.24	61.37	60.29	4.61
30	71.52	85.24	75.73	77.46	7.03
60	87.18	98.55	91.46	92.40	5.74
120	88.05	99.48	92.42	93.32	5.77
180	88.15	98.44	92.70	93.09	5.16
240	86.46	98.47	92.46	92.47	6.00
300	85.59	96.30	92.84	91.58	5.46
360	91.30	98.09	99.82	96.40	4.50

Wet granulation method

Time (min)	%Release				
	n 1	n 2	n 3	mean	SD
0	0.00	0.00	0.00	0.00	0.00
15	48.76	51.31	49.33	49.80	1.34
30	64.76	69.45	67.73	67.31	2.37
60	74.89	81.90	80.16	78.94	3.61
120	75.21	81.99	80.46	79.22	3.56
180	74.32	80.51	79.06	77.96	3.24
240	73.24	80.10	78.28	77.21	3.55
300	72.38	79.76	78.44	76.86	3.94
360	71.63	78.42	76.60	75.55	3.51

2. Effect of different polymers on drug release from sodium valproate matrix tablet by direct compression method

Ethylcellulose 5% w/w

Time (min)	%Release				
	n 1	n 2	n 3	mean	SD
0	0.00	0.00	0.00	0.00	0.00
15	55.23	64.24	61.37	60.29	4.61
30	71.52	85.24	75.73	77.46	7.03
60	87.18	98.55	91.46	92.40	5.74
120	88.05	99.48	92.42	93.32	5.77
180	88.15	98.44	92.70	93.09	5.16
240	86.46	98.47	92.46	92.47	6.00
300	85.59	96.30	92.84	91.58	5.46
360	91.30	98.09	99.82	96.40	4.50

Ethylcellulose 10% w/w

Time (min)	%Release				
	n 1	n 2	n 3	mean	SD
0	0.00	0.00	0.00	0.00	0.00
15	55.70	56.86	56.33	56.30	0.58
30	78.12	79.45	78.23	78.60	0.74
60	99.02	98.84	98.36	98.74	0.34
120	100.37	99.21	99.22	99.60	0.67
180	100.07	98.71	98.93	99.24	0.73
240	98.89	97.68	99.12	98.56	0.78
300	97.09	97.17	98.77	97.68	0.95
360	96.52	96.60	96.70	96.60	0.09

Ethylcellulose 15% w/w

Time (min)	%Release				
	n 1	n 2	n 3	mean	SD
0	0.00	0.00	0.00	0.00	0.00
15	49.94	52.71	47.59	50.08	2.56
30	65.08	72.86	69.07	69.00	3.89
60	89.32	88.48	88.92	88.91	0.42
120	90.51	88.53	88.92	89.32	1.05
180	89.05	87.48	88.65	88.40	0.81
240	89.45	86.96	88.69	88.37	1.28
300	87.71	87.07	87.87	87.55	0.42
360	87.44	86.60	88.29	87.44	0.85

Ethylcellulose 20% w/w

Time (min)	%Release				
	n 1	n 2	n 3	mean	SD
0	0.00	0.00	0.00	0.00	0.00
15	45.83	57.65	55.70	53.06	6.34
30	64.14	81.73	72.96	72.95	8.79
60	83.05	94.05	85.33	87.48	5.80
120	85.61	96.05	88.44	90.03	5.40
180	85.00	94.06	88.23	89.10	4.59
240	83.30	92.65	88.69	88.22	4.70
300	81.93	91.88	88.94	87.59	5.11
360	76.76	87.48	83.06	82.43	5.39

HPMC E4M 5%w/w

Time (min)	%Release				
	n 1	n 2	n 3	mean	SD
0	0.00	0.00	0.00	0.00	0.00
15	47.80	58.03	53.88	53.23	5.15
30	81.35	86.54	85.38	84.42	2.72
60	88.67	90.91	89.76	89.78	1.12
120	89.91	90.52	89.68	90.04	0.43
180	88.91	90.17	89.71	89.60	0.64
240	87.49	88.98	88.72	88.40	0.79
300	87.60	85.97	88.50	87.36	1.28
360	86.37	87.91	89.45	87.91	1.54

HPMC E4M 10%w/w

Time (min)	%Release				
	n 1	n 2	n 3	mean	SD
0	0.00	0.00	0.00	0.00	0.00
15	27.09	39.44	33.74	33.43	6.18
30	46.31	60.04	54.26	53.54	6.89
60	76.30	82.49	80.28	79.69	3.14
120	93.73	97.67	95.32	95.57	1.98
180	92.49	97.71	95.16	95.12	2.61
240	92.81	96.76	95.94	95.17	2.08
300	92.91	95.44	95.45	94.60	1.46
360	94.37	95.69	96.89	95.65	1.26

HPMC E4M 15%w/w

Time (min)	%Release				
	n 1	n 2	n 3	mean	SD
0	0.00	0.00	0.00	0.00	0.00
15	46.45	47.81	46.92	47.06	0.69
30	58.59	64.19	62.66	61.81	2.89
60	84.03	83.87	84.67	84.19	0.42
120	97.77	94.89	95.63	96.09	1.50
180	99.17	95.45	97.96	97.52	1.90
240	97.72	95.98	96.19	96.63	0.95
300	97.75	95.59	95.64	96.33	1.24
360	96.89	96.35	96.89	96.71	0.31

HPMC E4M 20%w/w

Time (min)	%Release				
	n 1	n 2	n 3	mean	SD
0	0.00	0.00	0.00	0.00	0.00
15	31.31	28.69	29.53	29.84	1.34
30	46.60	43.00	44.18	44.59	1.84
60	67.86	64.40	67.30	66.52	1.86
120	90.48	84.87	88.23	87.86	2.82
180	94.27	87.92	91.15	91.11	3.18
240	93.55	87.38	91.75	90.90	3.17
300	92.44	86.48	91.37	90.10	3.18
360	92.02	87.48	92.48	90.66	2.76

HPMC K15M 5%w/w

Time (min)	%Release				
	n 1	n 2	n 3	mean	SD
0	0.00	0.00	0.00	0.00	0.00
15	55.84	43.39	47.59	48.94	6.33
30	79.12	64.47	72.79	72.13	7.35
60	100.21	89.47	98.68	96.12	5.81
120	100.51	93.60	97.68	97.64	2.90
180	100.49	93.60	95.00	96.36	3.64
240	99.21	93.08	95.27	95.85	3.11
300	97.84	93.28	94.54	95.22	2.36
360	97.69	95.35	100.04	97.69	2.34

HPMC K15M 10%w/w

Time (min)	%Release				
	n 1	n 2	n 3	mean	SD
0	0.00	0.00	0.00	0.00	0.00
15	28.47	31.21	29.93	29.87	1.37
30	42.94	45.61	44.37	44.31	1.34
60	75.87	69.41	72.91	72.73	3.23
120	95.22	87.80	91.45	91.49	3.71
180	96.47	89.57	92.02	92.69	3.50
240	97.12	89.09	91.78	92.66	4.09
300	96.21	88.92	91.79	92.31	3.67
360	96.36	91.97	95.17	94.50	2.27

HPMC K15M 15%w/w

Time (min)	%Release				
	n 1	n 2	n 3	mean	SD
0	0.00	0.00	0.00	0.00	0.00
15	24.47	20.16	22.33	22.32	2.16
30	39.82	31.25	35.04	35.37	4.29
60	66.52	49.80	56.41	57.58	8.42
120	96.35	73.33	92.48	87.39	12.32
180	99.81	81.24	93.72	91.59	9.47
240	98.87	82.11	94.29	91.75	8.66
300	97.74	82.44	94.46	91.54	8.05
360	97.93	82.79	88.88	89.87	7.62

HPMC K15M 20%w/w

Time (min)	%Release				
	n 1	n 2	n 3	mean	SD
0	0.00	0.00	0.00	0.00	0.00
15	21.38	21.51	21.47	21.46	0.07
30	31.25	32.60	31.64	31.83	0.70
60	54.97	53.19	53.95	54.04	0.89
120	81.15	74.01	75.88	77.01	3.70
180	88.71	84.29	87.59	86.86	2.30
240	89.07	87.19	89.48	88.58	1.22
300	88.47	88.76	90.12	89.12	0.88
360	87.16	86.54	87.77	87.16	0.61

Xanthan gum 5%w/w

Time (min)	%Release				
	n 1	n 2	n 3	mean	SD
0	0.00	0.00	0.00	0.00	0.00
15	38.02	44.72	41.05	41.26	3.35
30	69.62	83.91	78.38	77.30	7.20
60	92.22	99.74	94.47	95.47	3.86
120	94.17	100.32	95.19	96.56	3.29
180	94.50	93.98	95.08	94.52	0.55
240	94.03	94.33	94.18	94.18	0.15
300	86.00	84.91	84.45	85.12	0.80
360	82.09	81.45	80.82	81.45	0.63

Xanthan gum 10%w/w

Time (min)	%Release				
	n 1	n 2	n 3	mean	SD
0	0.00	0.00	0.00	0.00	0.00
15	20.40	18.30	18.95	19.22	1.08
30	31.73	34.18	32.80	32.90	1.23
60	47.72	56.45	51.91	52.03	4.37
120	68.16	86.96	85.38	80.17	10.43
180	74.12	89.54	88.71	84.12	8.68
240	69.93	80.42	78.85	76.40	5.66
300	69.93	80.44	79.20	76.52	5.75
360	69.92	75.82	81.72	75.82	5.90

Xanthan gum 15%w/w

Time (min)	%Release				
	n 1	n 2	n 3	mean	SD
0	0.00	0.00	0.00	0.00	0.00
15	15.71	21.73	18.60	18.68	3.01
30	29.05	31.59	31.18	30.61	1.36
60	45.89	50.15	47.48	47.84	2.15
120	66.28	70.21	68.86	68.45	2.00
180	75.31	80.84	80.14	78.76	3.01
240	79.05	83.92	83.34	82.10	2.66
300	71.12	75.31	74.72	73.72	2.27
360	71.75	74.27	69.22	71.75	2.53

Xanthan gum 20%w/w

Time (min)	%Release				
	n 1	n 2	n 3	mean	SD
0	0.00	0.00	0.00	0.00	0.00
15	14.45	13.56	13.85	13.95	0.46
30	26.86	26.83	26.52	26.74	0.19
60	42.52	40.59	40.97	41.36	1.02
120	64.21	62.63	63.05	63.30	0.82
180	76.07	73.37	75.31	74.91	1.39
240	82.74	69.16	70.84	74.25	7.40
300	73.89	70.77	73.59	72.75	1.72
360	70.59	69.90	69.21	69.90	0.69

Carrageenan 5%w/w

Time (min)	%Release				
	n 1	n 2	n 3	mean	SD
0	0.00	0.00	0.00	0.00	0.00
15	63.38	58.93	62.37	61.56	2.34
30	87.10	81.57	82.41	83.70	2.98
60	88.88	84.14	83.84	85.62	2.83
120	88.60	84.45	85.02	86.02	2.25
180	86.43	81.92	82.76	83.71	2.40
240	87.63	81.36	82.33	83.77	3.37
300	84.13	81.04	81.87	82.34	1.60
360	84.05	83.68	84.43	84.05	0.37

Carrageenan 10%w/w

Time (min)	%Release				
	n 1	n 2	n 3	mean	SD
0	0.00	0.00	0.00	0.00	0.00
15	61.11	65.15	64.53	63.60	2.17
30	85.72	92.82	91.76	90.10	3.83
60	84.71	93.98	92.57	90.42	5.00
120	83.82	94.38	93.59	90.60	5.88
180	82.83	92.96	92.48	89.42	5.71
240	82.31	92.39	91.67	88.79	5.62
300	82.63	91.54	91.08	88.42	5.01
360	81.76	85.11	78.40	81.76	3.35

Carrageenan 15%w/w

Time (min)	%Release				
	n 1	n 2	n 3	mean	SD
0	0.00	0.00	0.00	0.00	0.00
15	82.51	65.77	72.92	73.73	8.40
30	92.87	86.60	88.56	89.34	3.21
60	91.42	85.93	88.43	88.59	2.75
120	90.17	85.08	88.02	87.76	2.55
180	91.15	84.81	87.53	87.83	3.19
240	89.34	83.79	87.11	86.75	2.80
300	87.86	82.49	85.91	85.42	2.72
360	86.33	81.46	76.58	81.46	4.88

Carrageenan 20%w/w

Time (min)	%Release				
	n 1	n 2	n 3	mean	SD
0	0.00	0.00	0.00	0.00	0.00
15	67.04	76.22	71.88	71.71	4.59
30	88.79	93.48	91.40	91.22	2.35
60	88.71	94.39	93.41	92.17	3.04
120	88.14	92.86	92.06	91.02	2.53
180	86.64	92.19	91.99	90.28	3.15
240	85.84	90.83	90.60	89.09	2.82
300	85.21	90.02	89.70	88.31	2.69
360	84.05	89.04	79.05	84.05	4.99

Sodium alginate 5%w/w

Time (min)	%Release				
	n 1	n 2	n 3	mean	SD
0	0.00	0.00	0.00	0.00	0.00
15	55.41	58.89	56.72	57.04	1.81
30	85.27	83.48	83.85	84.20	0.95
60	87.63	84.79	85.11	85.84	1.56
120	87.68	85.38	86.74	86.60	1.15
180	86.41	83.11	84.63	84.72	1.65
240	86.05	82.70	82.71	83.82	1.93
300	85.40	82.21	82.70	83.44	1.72
360	85.00	83.68	85.56	84.75	0.97

Sodium alginate 10%w/w

Time (min)	%Release				
	n 1	n 2	n 3	mean	SD
0	0.00	0.00	0.00	0.00	0.00
15	36.04	34.76	34.84	35.21	0.72
30	62.61	56.53	60.17	59.77	3.06
60	93.60	89.91	91.37	91.63	1.86
120	95.18	90.54	92.48	92.73	2.33
180	92.50	89.68	91.31	91.16	1.42
240	92.69	88.63	90.68	90.67	2.03
300	92.25	87.51	90.53	90.10	2.40
360	88.73	85.02	86.82	86.86	1.86

Sodium alginate 15%w/w

Time (min)	%Release				
	n 1	n 2	n 3	mean	SD
0	0.00	0.00	0.00	0.00	0.00
15	44.78	31.76	37.89	38.14	6.51
30	72.36	60.21	70.82	67.80	6.62
60	99.95	93.52	94.46	95.98	3.47
120	100.43	99.00	98.35	99.26	1.06
180	99.04	97.70	97.68	98.14	0.78
240	99.53	95.97	96.36	97.28	1.96
300	97.74	95.11	95.92	96.26	1.35
360	97.72	93.79	97.70	96.40	2.27

Sodium alginate 20%w/w

Time (min)	%Release				
	n 1	n 2	n 3	mean	SD
0	0.00	0.00	0.00	0.00	0.00
15	25.74	27.47	26.17	26.46	0.90
30	44.23	46.05	45.37	45.22	0.92
60	80.77	80.88	81.17	80.94	0.21
120	89.05	90.36	89.98	89.80	0.67
180	88.75	89.78	89.97	89.50	0.65
240	88.12	89.43	89.27	88.94	0.72
300	87.37	87.16	87.80	87.44	0.33
360	85.57	84.82	84.05	84.82	0.76

Kollidon® SR 5%w/w

Time (min)	%Release				
	n 1	n 2	n 3	mean	SD
0	0.00	0.00	0.00	0.00	0.00
15	63.99	67.81	66.63	66.14	1.95
30	85.03	87.78	85.90	86.24	1.41
60	96.82	95.16	96.07	96.02	0.83
120	97.44	96.34	91.24	95.01	3.31
180	95.89	94.95	91.17	94.00	2.50
240	94.66	93.65	90.51	92.94	2.16
300	93.95	92.56	90.10	92.20	1.95
360	94.94	93.12	91.80	93.29	1.58

Kollidon® SR 10%w/w

Time (min)	%Release				
	n 1	n 2	n 3	mean	SD
0	0.00	0.00	0.00	0.00	0.00
15	55.18	48.97	51.69	51.95	3.12
30	83.37	79.11	81.96	81.48	2.17
60	87.91	87.78	88.17	87.95	0.19
120	87.99	88.19	88.41	88.20	0.21
180	86.52	86.58	86.83	86.64	0.16
240	85.93	86.01	86.13	86.02	0.10
300	85.06	85.18	85.21	85.15	0.08
360	84.30	83.64	84.94	84.29	0.65

Kollidon® SR 15%w/w

Time (min)	%Release				
	n 1	n 2	n 3	mean	SD
0	0.00	0.00	0.00	0.00	0.00
15	48.24	53.63	50.43	50.77	2.71
30	78.87	88.95	85.38	84.40	5.11
60	86.76	93.29	91.40	90.48	3.36
120	86.11	92.19	90.75	89.68	3.17
180	87.19	91.29	90.53	89.67	2.18
240	85.80	90.53	89.41	88.58	2.47
300	84.30	89.45	89.34	87.70	2.94
360	81.82	84.35	82.30	82.82	1.34

Kollidon® SR 20%w/w

Time (min)	%Release				
	n 1	n 2	n 3	mean	SD
0	0.00	0.00	0.00	0.00	0.00
15	40.98	45.78	44.35	43.70	2.47
30	57.44	74.71	63.29	65.15	8.79
60	86.40	87.97	87.18	87.18	0.78
120	87.06	88.06	87.17	87.43	0.55
180	86.44	87.71	87.12	87.09	0.64
240	85.39	87.09	86.74	86.41	0.90
300	85.65	84.29	85.52	85.15	0.75
360	84.61	84.91	84.32	84.62	0.29

Eudragit® RSPO 5%w/w

Time (min)	%Release				
	n 1	n 2	n 3	mean	SD
0	0.00	0.00	0.00	0.00	0.00
15	62.01	58.02	58.24	59.42	2.25
30	79.28	73.88	75.73	76.29	2.74
60	90.94	82.52	85.08	86.18	4.32
120	91.97	82.92	86.76	87.22	4.54
180	90.69	82.31	85.91	86.30	4.21
240	89.56	80.53	85.34	85.14	4.52
300	88.96	80.42	85.07	84.82	4.27
360	90.79	83.82	89.57	88.06	3.72

Eudragit® RSPO 10%w/w

Time (min)	%Release				
	n 1	n 2	n 3	mean	SD
0	0.00	0.00	0.00	0.00	0.00
15	60.34	55.67	56.71	57.57	2.45
30	77.43	72.17	75.87	75.16	2.70
60	91.15	85.77	88.23	88.38	2.69
120	90.54	87.24	89.34	89.04	1.67
180	89.66	86.47	88.71	88.28	1.63
240	88.70	85.01	87.80	87.17	1.93
300	87.92	85.06	87.81	86.93	1.62
360	87.74	84.64	88.71	87.03	2.12

Eudragit® RSPO 15%w/w

Time (min)	%Release				
	n 1	n 2	n 3	mean	SD
0	0.00	0.00	0.00	0.00	0.00
15	54.64	53.69	53.62	53.98	0.57
30	71.24	71.95	72.28	71.82	0.53
60	86.84	87.81	87.54	87.40	0.50
120	87.38	88.61	88.23	88.08	0.63
180	87.39	86.75	87.81	87.32	0.53
240	86.07	85.22	86.97	86.09	0.87
300	85.07	84.90	86.82	85.60	1.06
360	84.44	84.56	84.68	84.56	0.12

Eudragit® RSPO 20%w/w

Time (min)	%Release				
	n 1	n 2	n 3	mean	SD
0	0.00	0.00	0.00	0.00	0.00
15	52.73	51.91	51.62	52.09	0.58
30	68.36	68.39	68.66	68.47	0.16
60	83.37	83.09	83.08	83.18	0.16
120	84.94	86.73	87.43	86.37	1.28
180	84.32	85.82	86.82	85.65	1.26
240	83.80	85.30	86.19	85.10	1.21
300	82.85	84.22	84.87	83.98	1.03
360	82.19	83.73	84.93	83.62	1.38

3. Effect of different polymers used in the outer layer on drug release from sodium valproate matrix

Ethylcellulose

Time (min)	%Release				
	n 1	n 2	n 3	mean	SD
0	0.00	0.00	0.00	0.00	0.00
15	16.89	17.98	17.46	17.44	0.54
30	25.37	27.67	26.52	26.52	1.15
60	41.41	52.14	46.92	46.82	5.36
120	67.14	93.13	79.08	79.79	13.00
180	82.27	94.26	81.95	86.16	7.01
240	83.10	93.02	82.75	86.29	5.83
300	81.82	92.20	82.35	85.46	5.85
360	81.30	91.42	82.58	85.10	5.51
420	80.31	90.53	81.93	84.26	5.50
480	80.17	89.84	81.79	83.93	5.18
540	78.74	88.12	81.10	82.65	4.88
600	78.21	88.44	80.82	82.49	5.32
660	78.73	88.53	81.52	82.93	5.05
720	81.83	90.60	84.93	85.79	4.45

HPMC K15M

Time (min)	%Release				
	n 1	n 2	n 3	mean	SD
0	0.00	0.00	0.00	0.00	0.00
15	18.40	17.85	17.97	18.07	0.29
30	27.66	31.48	28.86	29.33	1.95
60	39.99	50.95	47.48	46.14	5.60
120	72.11	73.99	73.19	73.10	0.95
180	81.20	86.84	85.33	84.46	2.92
240	85.73	90.20	88.29	88.07	2.24
300	85.63	89.62	88.17	87.80	2.02
360	85.49	88.52	87.87	87.29	1.59
420	84.62	88.79	88.25	87.22	2.27
480	85.55	87.51	88.08	87.05	1.33
540	84.17	87.34	88.01	86.51	2.05
600	82.39	85.80	86.67	84.95	2.26
660	81.74	84.96	85.55	84.08	2.05
720	80.93	84.86	86.19	83.99	2.74

4. Dissolution studies of mutilayer sustained release tablets of sodium valproate

Deionized water

Time (min)	%Release				
	n 1	n 2	n 3	mean	SD
0	0.00	0.00	0.00	0.00	0.00
15	8.77	8.28	7.60	8.22	0.59
30	11.75	12.92	13.70	12.79	0.98
60	18.93	21.36	23.54	21.28	2.30
120	30.21	33.20	37.13	33.15	3.47
180	38.76	41.81	42.78	41.12	2.09
240	43.93	48.32	48.92	47.06	2.72
300	48.69	53.34	55.42	52.48	3.45
360	53.67	59.27	62.68	58.54	4.55
420	59.81	66.09	70.21	65.37	5.24
480	66.23	72.18	77.49	71.97	5.64
540	70.50	74.27	81.50	75.42	5.59
600	72.74	78.96	86.05	79.25	6.66
660	76.14	83.09	91.18	83.47	7.53
720	79.51	86.34	94.53	86.79	7.52
900	84.62	91.12	102.45	92.73	9.02
1080	85.90	95.85	107.37	96.37	10.74
1260	89.40	95.95	105.96	97.10	8.34
1440	87.27	92.85	104.68	94.93	8.89

0.1 N HCl pH 1.2

Time (min)	%Release				
	n 1	n 2	n 3	mean	SD
0	0.00	0.00	0.00	0.00	0.00
15	1.37	1.31	1.43	1.37	0.06
30	1.59	2.22	2.11	1.98	0.34
60	3.18	4.49	3.36	4.68	1.60
120	6.76	10.46	8.50	8.58	1.85
180	9.88	14.20	12.31	12.13	2.16
240	14.48	17.01	17.19	16.23	1.51
300	17.43	19.45	19.40	18.76	1.15
360	18.03	21.40	20.64	20.02	1.77
420	24.71	22.33	22.03	23.02	1.47
480	23.24	24.64	25.45	24.45	1.12
540	26.27	26.82	26.35	26.48	0.30
600	28.94	29.02	25.10	27.69	2.24
660	28.94	29.16	27.01	28.38	1.18
720	28.36	29.78	29.31	29.15	0.73
900	32.79	33.25	30.52	32.19	1.47
1080	33.55	37.23	36.61	35.79	1.97
1260	37.37	40.04	37.47	38.29	1.51
1440	40.32	41.53	40.24	40.70	0.72

Phosphate buffer pH 6.8

Time (min)	%Release				
	n 1	n 2	n 3	mean	SD
0	0.00	0.00	0.00	0.00	0.00
15	8.81	9.56	7.85	8.74	0.86
30	13.15	13.64	12.37	13.06	0.64
60	20.83	21.91	23.62	22.12	1.41
120	31.93	31.46	33.67	32.36	1.16
180	37.48	38.05	41.41	38.98	2.13
240	42.95	44.31	50.14	45.80	3.82
300	48.43	49.37	52.97	50.26	2.40
360	53.10	54.94	60.06	56.03	3.61
420	58.92	60.04	64.36	61.11	2.87
480	63.85	63.80	71.06	66.24	4.18
540	70.07	67.72	74.59	70.79	3.49
600	71.76	70.81	76.03	72.87	2.78
660	77.53	73.11	81.30	77.31	4.10
720	81.61	76.99	83.06	80.55	3.17
900	86.69	81.15	88.61	85.48	3.88
1080	89.86	85.22	89.57	88.22	2.60
1260	93.89	86.18	93.27	91.11	4.29
1440	97.05	87.17	93.68	92.63	5.02

pH change (0.1 N HCl pH 1.2 followed by phosphate buffer pH 6.8)

Time (min)	%Release				
	n 1	n 2	n 3	mean	SD
0	0.00	0.00	0.00	0.00	0.00
15	2.77	2.18	2.28	2.41	0.32
30	3.61	4.20	4.44	4.08	0.43
60	4.03	5.31	5.81	5.05	0.92
120	8.36	10.82	13.65	10.95	2.62
180	11.91	16.57	14.82	14.43	2.36
240	23.62	24.38	25.36	24.46	0.87
300	30.30	30.88	32.56	31.25	1.18
360	35.97	36.56	38.17	36.90	1.14
420	43.67	40.49	43.67	42.62	1.84
480	50.36	46.74	49.23	48.78	1.85
540	56.82	51.50	54.46	54.26	2.67
600	61.18	55.67	59.27	58.71	2.80
660	66.31	60.19	62.68	63.06	3.08
720	69.91	63.21	67.18	66.77	3.37
900	80.05	75.47	76.08	77.20	2.49
1080	84.43	98.45	83.11	88.66	8.50
1260	86.69	82.53	85.63	84.95	2.16
1440	86.79	86.75	86.77	86.77	0.02

5. Dissolution studies of mutilayer sustained release tablets of sodium valproate combined with valproic acid

Deionized water

Time (min)	%Release				
	n 1	n 2	n 3	mean	SD
0	0.00	0.00	0.00	0.00	0.00
15	3.95	3.86	3.94	3.91	0.05
30	6.10	6.85	7.58	6.84	0.74
60	9.77	10.30	12.28	10.78	1.32
120	15.87	15.71	19.38	16.99	2.07
180	20.94	21.79	23.77	22.17	1.45
240	24.14	24.09	28.90	25.71	2.76
300	28.95	26.79	33.19	29.64	3.25
360	33.94	29.48	37.08	33.50	3.82
420	39.55	32.79	44.67	39.00	5.95
480	44.20	39.65	49.20	44.35	4.78
540	50.44	45.74	51.22	49.13	2.96
600	51.92	54.23	53.77	53.31	1.22
660	53.97	56.08	54.61	54.89	1.08
720	58.96	47.79	57.88	54.88	6.16
900	61.13	51.47	66.90	59.83	7.80
1080	66.57	56.51	69.01	64.03	6.63
1260	74.76	61.92	76.18	70.95	7.86
1440	85.95	82.31	89.34	85.87	3.51

0.1 N HCl pH 1.2

Time (min)	%Release				
	n 1	n 2	n 3	mean	SD
0	0.00	0.00	0.00	0.00	0.00
15	1.05	1.07	1.05	1.06	0.01
30	1.93	1.66	1.66	1.75	0.16
60	3.65	3.41	3.11	3.39	0.27
120	6.15	6.22	5.67	6.02	0.30
180	8.14	8.14	7.27	7.85	0.51
240	9.45	9.98	8.70	9.37	0.65
300	10.78	10.64	9.72	10.38	0.58
360	11.98	12.17	11.57	11.91	0.31
420	12.72	13.17	12.60	12.83	0.30
480	13.87	14.33	13.30	13.83	0.52
540	14.71	15.06	14.88	14.88	0.17
600	15.48	15.22	15.67	15.46	0.22
660	15.92	16.32	15.81	16.01	0.27
720	16.08	16.63	16.49	16.40	0.28
900	18.34	19.16	19.00	18.84	0.43
1080	20.64	21.55	21.23	21.14	0.46
1260	23.08	23.90	23.58	23.52	0.41
1440	26.24	27.05	26.61	26.64	0.41

Phosphate buffer pH 6.8

Time (min)	%Release				
	n 1	n 2	n 3	mean	SD
0	0.00	0.00	0.00	0.00	0.00
15	5.14	4.39	3.98	4.50	0.59
30	7.35	6.92	6.43	6.90	0.46
60	11.45	10.99	9.94	10.79	0.77
120	17.96	18.88	16.08	17.64	1.43
180	23.81	23.90	20.63	22.78	1.87
240	28.46	28.74	25.17	27.46	1.99
300	32.01	33.03	28.70	31.25	2.27
360	36.54	37.58	32.73	35.61	2.55
420	40.11	41.52	36.75	39.46	2.45
480	43.99	45.50	39.48	42.99	3.14
540	46.00	49.09	42.93	46.01	3.08
600	49.68	51.55	45.53	48.92	3.08
660	52.10	54.85	49.44	52.13	2.71
720	55.32	57.71	50.92	54.65	3.44
900	64.03	65.52	57.51	62.35	4.26
1080	70.60	70.01	62.09	67.57	4.75
1260	72.67	74.13	66.05	70.95	4.31
1440	77.92	79.27	72.96	76.72	3.32

pH change (0.1 N HCl pH 1.2 followed by phosphate buffer pH 6.8)

Time (min)	%Release				
	n 1	n 2	n 3	mean	SD
0	0.00	0.00	0.00	0.00	0.00
15	0.74	0.93	0.96	0.88	0.12
30	1.08	1.55	1.96	1.53	0.44
60	2.87	2.63	2.87	2.79	0.13
120	5.18	5.58	5.17	5.31	0.23
180	5.18	5.97	6.56	5.90	0.69
240	7.39	9.84	11.87	9.70	2.24
300	11.36	16.23	17.05	14.88	3.08
360	15.00	20.47	20.21	18.56	3.09
420	20.02	24.66	25.61	23.43	2.99
480	23.12	26.78	28.15	26.12	2.60
540	26.54	31.20	31.82	29.85	2.89
600	29.30	34.79	37.90	34.00	4.36
660	32.72	38.46	41.22	37.46	4.34
720	35.67	41.29	42.76	39.90	3.74
900	41.17	50.07	52.07	47.77	5.82
1080	49.23	54.86	61.27	55.19	5.93
1260	53.05	59.37	66.24	59.55	6.60
1440	63.01	68.58	75.50	69.03	6.26

6. Dissolution studies of Encorate Chrono®

0.1 N HCl pH 1.2

Time (min)	%Release				
	n 1	n 2	n 3	mean	SD
0	0.00	0.00	0.00	0.00	0.00
15	1.33	1.45	1.88	1.55	0.29
30	3.27	3.46	3.64	3.46	0.18
60	6.32	6.57	6.61	6.50	0.16
120	10.65	10.35	10.59	10.53	0.16
180	15.30	14.41	14.78	14.83	0.45
240	17.14	17.00	17.44	17.20	0.22
300	19.37	19.28	19.82	19.49	0.29
360	21.46	20.96	21.50	21.31	0.30
420	22.95	22.69	23.24	22.96	0.27
480	24.31	23.94	24.32	24.19	0.22
540	24.68	24.94	25.83	25.15	0.60
600	26.47	26.58	27.12	26.72	0.35
660	28.67	28.86	29.41	28.98	0.38
720	30.27	30.60	30.08	30.32	0.26
900	32.82	32.35	33.09	32.76	0.37
1080	37.03	35.76	38.89	37.22	1.57
1260	39.93	38.33	45.75	41.34	3.91
1440	40.27	39.06	45.87	41.73	3.63

Phosphate buffer pH 6.8

Time (min)	%Release				
	n 1	n 2	n 3	mean	SD
0	0.00	0.00	0.00	0.00	0.00
15	9.48	8.48	9.15	9.04	0.51
30	14.12	16.29	16.66	15.69	1.37
60	24.03	23.48	23.11	23.54	0.46
120	32.66	31.84	32.73	32.41	0.49
180	39.32	39.62	40.48	39.81	0.60
240	45.29	44.81	45.28	45.13	0.27
300	48.62	49.31	50.22	49.38	0.81
360	52.12	52.97	53.06	52.72	0.51
420	54.94	56.03	56.85	55.94	0.96
480	61.44	62.01	62.68	62.04	0.62
540	63.67	64.03	64.66	64.12	0.50
600	64.12	65.53	66.51	65.38	1.20
660	65.85	63.05	63.70	64.20	1.47
720	62.66	63.72	64.21	63.53	0.79
900	64.91	68.69	70.72	68.10	2.95
1080	71.40	72.50	73.56	72.79	1.08
1260	72.75	74.32	75.67	74.25	1.46
1440	76.10	77.74	79.91	77.91	1.91

pH change (0.1 N HCl pH 1.2 followed by phosphate buffer pH 6.8)

Time (min)	%Release				
	n 1	n 2	n 3	mean	SD
0	0.00	0.00	0.00	0.00	0.00
15	1.79	1.92	1.67	1.79	0.13
30	3.34	3.67	3.03	3.35	0.32
60	6.13	6.68	6.90	6.57	0.39
120	10.62	10.37	10.45	10.48	0.13
180	9.30	10.22	8.77	9.43	0.74
240	17.59	18.52	18.25	18.12	0.48
300	25.22	25.05	25.50	25.26	0.23
360	30.31	30.96	30.65	30.64	0.32
420	34.72	34.66	36.59	35.32	1.10
480	38.78	39.50	38.55	38.94	0.49
540	43.20	41.74	42.64	42.52	0.73
600	45.67	43.87	45.17	44.90	0.93
660	45.43	43.31	47.43	45.39	2.06
720	47.80	45.07	45.98	46.28	1.39
900	51.89	49.54	50.38	50.60	1.19
1080	52.55	53.42	54.53	53.50	0.99
1260	55.37	56.80	57.60	56.59	1.13
1440	58.21	59.89	61.58	59.89	1.68

7. Dissolution studies of Depakine Chrono®

0.1 N HCl pH 1.2

Time (min)	%Release				
	n 1	n 2	n 3	mean	SD
0	0.00	0.00	0.00	0.00	0.00
15	1.13	1.19	1.08	1.13	0.06
30	2.42	2.50	3.04	2.65	0.34
60	4.50	4.55	5.39	4.81	0.50
120	7.98	7.77	8.93	8.23	0.62
180	11.18	10.55	12.30	11.35	0.89
240	14.15	13.36	15.76	14.43	1.23
300	17.06	15.89	18.33	17.09	1.22
360	20.49	19.76	22.16	20.80	1.23
420	23.42	22.71	25.11	23.75	1.23
480	26.84	25.79	26.47	26.36	0.53
540	28.74	27.53	29.58	28.62	1.03
600	30.62	29.40	31.07	30.37	0.86
660	30.84	30.61	32.56	31.34	1.07
720	33.17	32.32	34.28	33.26	0.98
900	36.16	35.62	37.86	36.55	1.17
1080	39.26	38.60	40.99	39.62	1.24
1260	41.64	40.85	43.30	41.93	1.25
1440	44.49	44.31	46.16	44.99	1.02

Phosphate buffer pH 6.8

Time (min)	%Release				
	n 1	n 2	n 3	mean	SD
0	0.00	0.00	0.00	0.00	0.00
15	8.27	8.45	9.04	8.58	0.40
30	13.05	12.91	13.07	13.01	0.09
60	20.65	19.98	20.08	20.23	0.36
120	30.26	30.67	30.20	30.38	0.26
180	38.83	40.22	39.25	39.43	0.71
240	46.73	46.70	45.36	46.26	0.78
300	52.97	52.49	50.71	52.05	1.19
360	58.23	56.82	54.89	56.65	1.68
420	61.26	61.12	59.37	60.59	1.06
480	63.88	63.52	60.82	62.74	1.67
540	66.16	65.16	62.94	64.75	1.65
600	67.99	66.69	64.57	66.42	1.72
660	69.04	67.59	65.96	67.53	1.54
720	70.56	68.05	66.44	68.35	2.08
900	72.17	70.36	69.55	70.69	1.34
1080	73.59	72.51	70.40	72.17	1.62
1260	74.55	74.12	72.32	73.67	1.18
1440	77.33	76.84	76.32	76.83	0.50

pH change (0.1 N HCl pH 1.2 followed by phosphate buffer pH 6.8)

Time (min)	%Release				
	n 1	n 2	n 3	mean	SD
0	0.00	0.00	0.00	0.00	0.00
15	1.30	1.68	0.79	1.26	0.45
30	2.23	2.47	2.11	2.27	0.18
60	3.61	4.68	4.32	4.20	0.55
120	7.05	8.19	7.79	7.68	0.57
180	14.45	13.90	13.53	13.96	0.46
240	20.67	22.12	21.01	21.27	0.76
300	26.96	28.60	27.71	27.76	0.82
360	33.49	34.13	32.65	33.42	0.75
420	37.36	39.24	37.72	38.11	1.00
480	42.37	44.02	42.21	42.87	1.01
540	47.42	47.56	46.23	47.07	0.73
600	49.97	51.06	48.16	49.73	1.46
660	53.12	52.98	50.99	52.37	1.19
720	55.13	54.67	52.79	54.20	1.24
900	58.87	58.37	58.15	58.46	0.37
1080	62.42	60.51	60.29	61.07	1.17
1260	64.54	62.08	61.80	62.81	1.51
1440	65.62	64.72	63.81	64.72	0.91

VITA

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