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Worawan Saingam

Poj Kulvanich

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Worawan Saingam and Poj Kulvanich

Department of Pharmaceutics and Industrial Pharmacy, Faculty of Pharmaceutical Sciences, Chulalongkorn University, Bangkok, Thailand 10330

KEYWORDS: sodium valproate, valproic acid, matrix tablet, sustained release, multilayer tablet

INTRODUCTION

Nowadays, sodium valproate and valproic acid commercial products are available in different dosage forms; tablet, enteric-coated tablet, delayed-release tablet, capsule (liquid-filled), sprinkle, solution, intravenous, suppositories. All dosage forms provide 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, it is of interest to develop multilayer sustained release tablet formulation of sodium valproate and valproic acid that provides a viable resolution for delivering active ingredients using a cost-effective technology.

MATERIALS AND METHODS

Materials

Sodium valproate, valproic acid, HPMC K15M (Methocel K15M), dibasic calcium phosphate, colloidal silicon dioxide, talcum, trifluoroacetic acid, potassium dihydrogen orthophosphate, acetonitrile, methanol, sodium hydroxide and hydrochloric acid

Methods

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 Table 1. Valproic acid was first mixed with colloidal silicon dioxide which used as absorbent, then mixed with all ingredients. Trilayer tablets were prepared by compressing the powder mixture 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. The multilayer tablets were evaluated for drug release and amount of drug release were assayed using validated HPLC method.

Table 1 Formula of multilayer tablets

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	

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

Drug content of the mutilayer 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. 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.

Dissolution studies

Drug release study was performed using USP apparatus I (basket) dissolution tester, operating at 100 rpm. Dissolution test was performed in 900 ml of deionized water, 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 withdrawn at 15, 30 minutes, every 1 hour until 12 hours and every 3 hours 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 HPLC by autosampler and peak areas were measured.

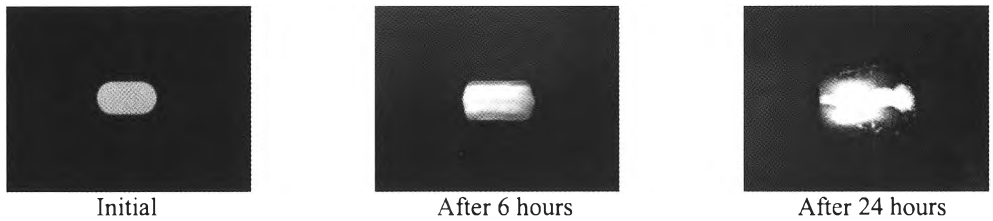
RESULTS AND DISCUSSION

Design of multilayer 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.

Dissolution studies

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 exposure to dissolution medium, the two outer layers swell to form gelled layers surrounding the lateral side of the inner layer rapidly (Figure 1), thereby effectively control the releases of drug from the inner immediate-release layer (Park et al., 2010). HPMC K15M was used as a swellable polymer. After multilayer tablet exposed to various dissolution media such as deionized water, 0.1 N HCl pH 1.2, phosphate buffer pH 6.8 and pH change, 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 as presented in Figure 2.



Initial After 6 hours After 24 hours

Figure 1 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 in phosphate buffer pH 6.8

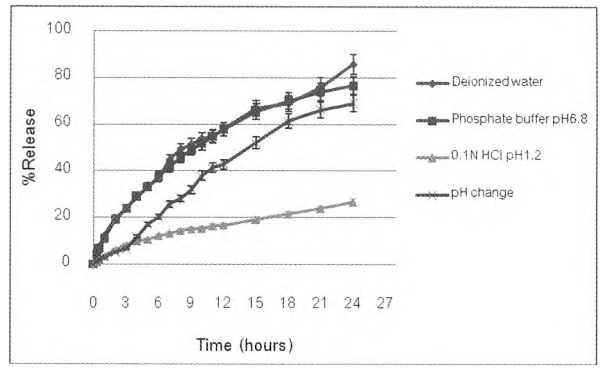
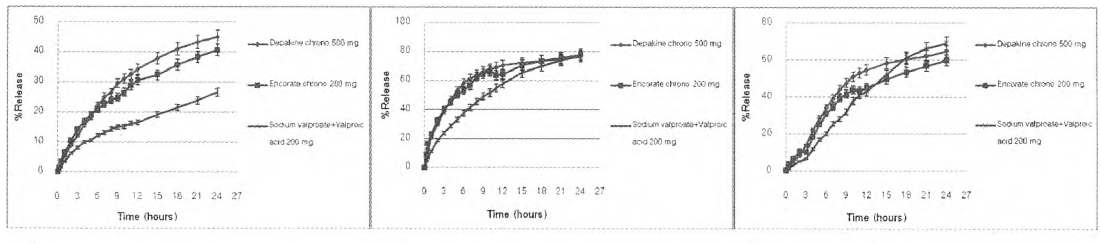


Figure 2 Dissolution profiles of multilayer sustained release tablets of sodium valproate combined with valproic acid in various dissolution media such as deionized water, 0.1 N HCl pH 1.2, phosphate buffer pH 6.8 and pH change (0.1 N HCl pH 1.2 followed by phosphate buffer pH 6.8)

The pH of dissolution medium were increased, the drug release rate was obviously increased. pH of dissolution medium had appreciable effect on drug release. The drug release at 24 hours was in the rank order of 85.87% in deionized water, 76.72% in phosphate buffer pH 6.8, 69.03% in pH change and 26.64% in 0.1 N HCl pH 1.2. 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), therefore, exhibited slow dissolution characteristics.

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



[a] [b] [c]

Figure 3 Comparison dissolution profiles of developed product with two commercial products in [a] 0.1 N HCl pH1.2 [b] phosphate buffer pH 6.8 and [c] pH change

Depakine chrono® and Encorate chrono® were prepared as matrix system, which release the drug in continuous manner. These released 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. As a result, multilayer sustained release tablets of sodium valproate combined with valproic acid formulation could exhibited drug release similar to Depakine chrono® and Encorate chrono® in phosphate buffer pH 6.8 and pH change but much slower in 0.1 N HCl pH1.2, which affected by the low solubility of valproic acid in acid medium.

CONCLUSIONS

In conclusions, the drug released from multilayer formulations were sustained for 24 hours. Dissolution of multilayer sustained release tablets of sodium valproate combined with valproic acid was obviously increased as the pH of dissolution medium were increased.

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