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PREPARATION AND EVALUATION OF CONTROLLED-RELEASE SODIUM VALPROATE / VALPROIC ACID (VALDISOVAL) TABLETS

Sayed H. Khidr

Department of Industrial Pharmacy, Faculty of Pharmacy, Assiut University, Assiut, Egypt.

دواء الفالديزوفال يتكون من خليط من مادتى فالبروات الصوديوم وحمض الفالبرويك بنسبة ١:٢ ويستخدم كمضاد للصرع ٠فى هذا البحث تم تحضير أقراص متحكمة الآنطلاق من هذا العقار وذلك لتفادى التناول المتكرر للدواء بطريقتى الكبس المباشر والتحبب الرطب٠ ونظرا لأن العقار موضوع الدراسة شره لامتصاص الماء مما يتعذر معه صياغته فى شكل أقراص فلقد استخدمت مادتى ثنائى أكسيد السيلكون وسيلكات الكالسيوم لإمكانية عمل أقراص من هذا العقار. ولقد استخدمت الصواغات التاليـــة مصاحبة للعقار: ايدراجيت رقمى RSPO , RLPO كصواغات للكبس المباشر وللتحكم فى الاتاحة٠ أما بالنسبة لطريقة التحبب الرطب فى تحضير الاقراص فقد تم استخدام ايثيل سليلوز وايدروكس بروبيل ميثيل سليلوز أو ايدروكس ايثيل سليلوز كمواد تتحكم فى الإنطلاق مع مواد رابطة معينة مذابة فى الماء أو الكحول٠ ولقد قيمت الأقراص المحضرة بهاتين الطريقتين فى النواحى التاليه : الخواص الفيزيائية للاقراص مثل الصلابة والهشوشة وتجانس الوزن والسمك وكذلك الاتاحة المعملية باستخدام جهاز الاتاحة المعملية "٢" المطابق لدستور الادوية الامريكى وذلك لمدة ثمان ساعات فى أوساط اتاحة معينة. وقد وجد أن زيادة نسبة البوليمرات قللت معدل الإتاحة المعملية للعقار. ولقد قورنت نتائـــج إتاحة الأقراص المحضرة بأقراص مشابهة متواجدة بالسوق الدوائى ووجدت النتائـــج متشابهة مع بعض الاقراص المحضرة. ولقد أخضعت الاقراص المتشابهة فى الإتاحة لأقراص السوق لمزيد من التعامل ، حيث تم كسوتها باستخدام بوليمر ايدراجيت L100-55. وعند دراسة حركية معدل الإتاحة للعقار من هذه الاقراص فى وسط حمضى يتبعه وسط قاعدى ومقارنتها مع أقراص السوق تحت نفس الظروف وجد أن نتائج الإتاحة المعملية متشابهة الى حد كبير ، كما وجد أن معدل الاتاحة يتبع معادلة رتبة الصفر.

Valdisoval (VL) is a mixture of sodium valproate (SV) and valproic acid (VA) in a 2:1 ratio. Different polymers were used to develop a controlled-release tablet formulation for VL using either direct compression or wet granulation techniques. Eudragits RSPO and RLPO in different concentrations were used as direct compression and rate controlling polymers, while ethyl cellulose (EC), hydroxy propyl methyl cellulose (HPMC) and hydroxy ethyl cellulose (HEC) were used as release retardants in the wet granulation matrix formulations. Tablets prepared showed good physical properties; e.g. hardness, friability, weight variations, using different polymers by direct compression and wet granulation techniques. The release profile of SV from the compressed tablets was studied using the USP dissolution apparatus II at 100 rpm in either distilled water for 8 hours or in 0.1 N HCl for one hour followed by phosphate buffer, pH 6.8 for another 7 hours. Sodium valproate release was found to decrease by increasing the concentration of Eudragit RSPO in the formula and was less affected by the concentration of Eudragit RLPO.The release of SV from the tablets containing ethyl cellulose as tablet matrix was affected by the type of the binder in the wet granulation process. This was indicated by the difference in $T_{50\%}$ (time for 50% of the drug to be released). HEC was used as a release retardant in a concentration range 10 to 25% w/w. The release of SV from these tablets was inversely proportional to HEC concentration in the formula.Tablets containing 12.5% w/w of this polymer were film coated using Eudragit L100-55.When the release profile of SV from these tablets was compared to a marketed product (Depakine Chrono^{R}) under the same conditions, an almost identical dissolution pattern was found. Zero order release kinetics was elucidated from the dissolution data.

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INTRODUCTION

Valdisoval (VL) is a mixture of Sodium Valproate (SV) and Valproic acid (VA) in a 2: 1 ratio. Sodium Valproate and Valproic acid are widely used for the treatment of epileptic seizures or convulsions.[1] Valproic acid is a liquid at room temperature and this makes it difficult to formulate and manufacture in a solid dosage form. Sodium Valproate, on the other hand, is an extremely hygroscopic, deliquescent and freely water soluble solid substance. It absorbs water from the atmosphere at a relative humidity of above 44% at 20°,[2] resulting in processing problems during tablet production. Although many new antiepileptic drugs have been recently developed,[3,4] Valproate remains among the most effective and widely spread drugs used in a wide variety of partial and generalized seizures.[5] However, despite its efficacy in the treatment of epilepsy, VA has a relatively short and variable elimination half-life. Reported half-lives have ranged from about 5 to 20 hours.[1] This leads to substantial fluctuations in the drug plasma concentration, especially in chronic administration. To maintain a stable plasma level, it is necessary to give the drug more frequently (3 or 4 times/day). This results in lower compliance with the prescribed dosing regimen. Moreover, widely fluctuating plasma levels result in either a less than therapeutic or too large amounts of the drug.

Controlled-release solid dosage formulations have been developed using either SV alone[6,7] or VA[8,9] or SV:VA (1:1) complex (Divlproex sodium).[10]

The purpose of this study is to develop a controlled-release sodium valproate tablet formulation using Valdisoval as the active ingredient. The effect of formulation variables on the in-vitro dissolution was studied. The in-vitro release profile of the developed formula was compared to that of a marketed product (Depakine Chrono^{R}).

EXPERIMENTAL

Materials

Valdisoval (Katwijk-Chemie BV, The Netherlands); Eudragit acrylic polymers RSPO, RLPO and L100-55 (Rohm GmbH, Darmstadt, Germany); Hydroxy ethyl cellulose (HEC) (Natrosol 250 HHX) (Hercules, Wilmington, DE, USA); Ethyl cellulose (EC) (Dow chemical, Midlands MI, USA); Hydroxy propyl methyl cellulose (HPMC) (Methocel E15) (Dow chemical, Midland, MI, USA); Calcium silicate (Kirsch Pharma GmbH, Germany); Polyethylene glycol (PEG) 6000 (E. Merck, Darmstadt, Germany); Colloidal silicon dioxide (Aerosil 200, Degussa, Germany); Polyvinyl pyrrolidone USP (PVP; Plasdone GAF / ISP, Wayne, NJ, USP); Magnesium stearate (BDH Ltd., Poole, England); Talc (Luna, Cairo, Egypt); Acetonitrile (HPLC grade) (Fisher Scientific, Springfield, NJ, USA); Dibasic calcium phosphate (Rhone - Poulenc, Shelton, CT, USA). All other materials were of analytical reagent grade and were used as received.

Method

Tablets formulation and method of preparation: Tablet cores

Three approaches were used for the formulation and preparation of sodium Valproate controlled release matrix tablets.

1. A direct compression technique using Eudragit acrylic polymers: (Table 1).
   In this method, the drug, Eudragit polymers, dibasic calcium phosphate and colloidal silicon dioxide(Aerosil 200) were mixed together in a cube mixer (Erweka, KB15, Germany). Talc powder was added and mixed for 10 minutes. Magnesium stearate was then added and mixed for 5 minutes. The blend was compressed into tablets at hardness of 7 - 10 kp.
2. A wet granulation technique using ethyl cellulose as a controlled release polymer with different binders: (Table 2).
   The drug was dry mixed with ethyl cellulose and calcium silicate in a cube mixer and the mixture was granulated using an aqueous solution of the appropriate binder in the formula. The wet mass was passed through 1.6 mm standard sieves (Retsch Co., Germany), dried in a tray oven (Hereus, Germany) at 50-55° for about three hours to moisture content of 1-2%. The dried granules were passed through 1.0 mm screen, mixed with colloidal silicon dioxide and talc powder for 10 minutes. Magnesium stearate was then added and mixed for

Table 1: Direct compression Valdisoval tablet formulation.

Material	Formulation (% w/w)				
	1	2	3	4	5
Valdisoval	71.50	69.50	68.00	68.50	66.50
Eudragit RSPO	17.00	21.00	25.00	21.00	21.00
Eudragit RLPO	0.50	0.50	0.50	2.50	0.50
Diabasic calcium phosphate	6.00	4.00	1.50	3.00	7.00
Colloidal silicon dioxide	3.0	3.00	3.00	3.00	3.00
Talc powder	1.50	1.50	1.50	1.50	1.50
Magnesium stearate	0.50	0.50	0.50	0.500	0.50

Table 2: Wet granulation Valdisoval tablet formulation using ethyl cellulose.

Material	Formulation (% w/w)			
	6	7	8	9
Valdisoval	64.00	63.00	70.00	65.00
Ethyl cellulose	20.00	20.00	20.00	25.00
HPMC E 15	-	10.00	-	-
Eudragit NE-30D	-	-	3.00	3.00
Dibasic calcium phosphate	9.00	-	-	-
Calcium silicate	3.00	3.00	3.00	3.00
Colloidal silicon dioxide	2.00	2.00	2.00	2.00
Talc powder	1.50	1.50	1.50	1.50
Magnesium stearate	0.50	0.50	0.50	0.50

Table 3: Wet granulation Valdisoval tablet formulation using hydroxy ethyl cellulose.

Material	Formulation (% w/w)				
	10	11	12	13	14
Valdisoval	66.50	70.50	74.50	76.50	79.00
Hydroxy ethyl cellulose	25.00	21.00	17.00	15.00	12.50
PVP K25	1.50	1.50	1.50	1.50	1.50
Calcium silicate	3.00	3.00	3.00	3.00	3.00
Colloidal silicon dioxide	2.00	2.00	2.00	2.00	2.00
Talc powder	1.50	1.50	1.50	1.50	1.50
Magnesium stearate	0.50	0.50	0.50	0.50	0.50

5 minutes. The blend was compressed into tablets at hardness of 12-16 kp.

3. A wet granulation technique using hydroxy ethyl cellulose: (Table 3).
   In this case, the drug was dry mixed with the HEC at certain ratio. The mixture was granulated with a solution of polyvinyl pyrrolidone (PVP) either in alcohol (Isopropanol) or in water. The wet granules were dried to 1-2% moisture content, passed through 1.0 mm screen and mixed with colloidal silicon dioxide and talc powder for 10 minutes. Magnesium stearate was then added and mixed for 5 minutes. The mixture was compressed into tablets at hardness of 10 - 14 kp.

Tablets coating

Core tablets from selected batches were coated using the coating formula shown in Table (4). The coating solution was sprayed on the tablet cores in a laboratory size coating pan (Erweka, type DKE), using a spray gun with a 2 mm spray nozzle orifice and a source of hot air. The pan was set at an angle of 30C° and was rotated at 30 to 40 rpm.

Table 4: Coat formula

Material	% w/w
Eudragit L100-55	7.35
Polyethylene glycol 6000	2.50
Titanium dioxide	3.00
Glycerol 99.5 %	1.50
Talc powder	2.25
Magnesium stearate	0.75
Isopropanol to	100.00

Tablet compression

Tablets from all formulations were compressed by Erweka tablet press, type TBR10 using oblong 17 × 8 mm tooling. Tablet weight varied according to each formula. Tablets were within ± 5.0% of their theoretical weight.

Release studies

The release profile of sodium valproate from compressed tablets was studied using USP XXIV dissolution apparatus II (paddle) at 100 rpm (Erweka, Model DT 70). The dissolution medium was 900 ml of either distilled water for 8 hours or 0.1 N HCl for one hour followed by phosphate buffer solution (pH 6.8) for another 7 hours. The dissolution medium was adjusted and maintained at 37° ± 0.5°. A 0.5 ml sample was withdrawn after 1, 2, 3, 4, 5, 6, 7 and 8 hours and the volume was immediately replaced with fresh dissolution media heated at 37°. Sodium valproate was determined on filtered samples using an HPLC method (see assay). Six individual tablets were used and the average valproate percent released was calculated. The dissolution of the brand sample was run parallel to Valdisoval tablets for comparison.

Assay

Sodium valproate was determined by a developed and validated HPLC assay using HP 1100 (Hewlet Packard, USA) with variable wavelength detector, autosampler and Hypersil C18 column (4.6 × 250 mm, 5 µm). The mobile phase composed of 40:60 acetonitrile: phosphate buffer, pH 3.0. The λ_{max} was 220 nm and the injection volume was 50 µl at flow rate 1.5 ml/min.

Data Treatment

To elucidate the mechanism of drug release, fractional release was fitted to a power law equation.[11]

$$M_t / M_\infty = Kt^n$$

Where M_t is the amount of drug released at time t, M_∞ is the amount of label claim, K is the release rate constant and n is an exponent describes the drug release. For n = 0.5, the release mechanism follows the square root of time and for n approaches 1 the release rate follows zero order kinetics, this equation is applied for $M_t / M_\infty \leq 0.8$.[12]

RESULTS AND DISCUSSION

The preparation of controlled release (CR) formulation for Valdisoval tablets has two main aspects; first to control the release of SV, which is a freely water soluble material and second to protect the tablet from the moisture in the surrounding environment because of the high hygroscopic properties of the active material. For the first point, different polymers with known retarding effects were used. As for the second point, relatively high concentrations

of colloidal silicon dioxide and talc powder were used in all formulations. In addition, calcium silicate at 3.0% w/w was used in some formulations. With this combination, it was possible to keep the compressed tablets in a dry condition for approximately one month before applying a protective coat.

The physical characteristics of Valdisoval tablets prepared by three approaches together with $T_{50\%}$ (time for 50% of the drug to be released) are shown in Table 5. From this table it can be shown that the hardness of directly compressed tablets is less than that of tablets compressed using wet granulation. Within this group of tablets, an increase in hardness affects the release of SV, which was reflected in an increase in $T_{50\%}$. Incorporating HPMC with EC increased the hardness (formula 7), while dibasic calcium phosphate decreases the hardness (formula 6). Dibasic calcium phosphate can be used to retard the release of highly water-soluble drugs.[13] The smaller $T_{50\%}$ for formula 6 compared to formula 7 can be attributed to the difference in hardness. The higher hardness values for HPMC containing tablets may be due to the recrystallization of HPMC and/or the drug in the tablet void spaces.[14]

The release profiles of Valdisoval tablets compressed using three different approaches are shown in Figures 1 to 3. Figure 1 shows the effect of Eudragit RSPO concentration on the dissolution of directly compressed Valdisoval tablets in water. Each data point represents the mean of at least 6 determinations. Eudragits RSPO and RLPO are directly compressible powder form of Eudragit RS and RL, respectively. The required polymer quantities for directly compressed matrix tablets are between 10 and 50% of the tablets weight. Good quality tablets were produced using RSPO at a concentration range from 17 to 25%. The drug release retardant effect was found to increase with increasing Eudragit RSPO concentration in the formula. This is expected because of the lower permeability of Eudragit RSPO to the active ingredient. On the other hand, increasing the concentration of Eudragit RLPO from 0.5 to 2.5% did not affect the release pattern of Valdisoval tablets significantly (formula 4).

Figure 2 shows the dissolution profile of Sodium Valproate from Valdisoval matrix tablets compressed using wet granulation technique and ethyl cellulose as the controlled-release polymer. The tablets were coated using Eudragit L100-55, which forms an enteric polymer film that dissolves at pH 5.5. The

Table 5: Characteristics of the prepared Valdisoval controlled-release tablets.

Formula	Weight (mg)* ± (SD)	Thickness (mm)* ± (SD)	Hardness (kp)** ± (SD)	Friability %	$T_{50\%}$ (min)
1	677 (0.022)	5.31 (0.10)	7.8 (0.95)	0.44	51.0
2	700 (0.015)	5.31 (0.10)	9.9 (1.28)	0.50	90.0
3	746 (0.016)	5.58 (0.07)	10.11 (1.33)	0.28	115.0
6***	747 (0.017)	5.53 (0.08)	12.5 (1.25)	0.31	135.0
7***	762 (0.014)	5.76 (0.06)	17.3 (1.18)	0.06	185.0
8***	727 (0.015)	5.45 (0.08)	16.2 (0.45)	0.07	225.0
10	726 (0.016)	7.32 (0.07)	10.5 (0.59)	0.39	325.0
11	682 (0.017)	7.10 (0.06)	11.0 (0.47)	0.35	290.0
12	648 (0.015)	6.55 (0.07)	10.9 (0.52)	0.12	275.0
13	633 (0.014)	6.51 (0.04)	12.3 (0.63)	0.05	255.0
14	615 (0.05)	6.57 (0.03)	13.01 (0.71)	0.08	240.0

* Mean of 20 tablets
** Mean of 6 tablets
*** Coated tablets

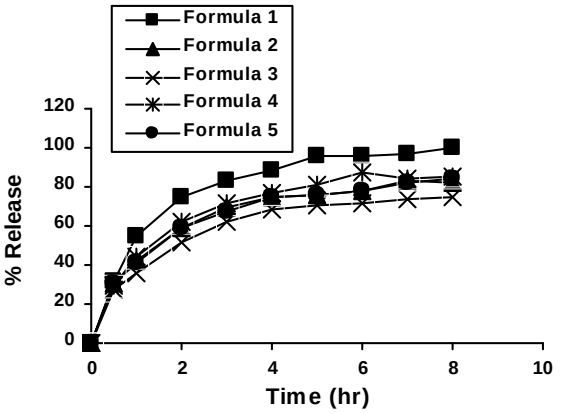

Fig. 1: Effect of Eudragit polymers concentration on the release profile of SV from Valdisoval core tablets in water.

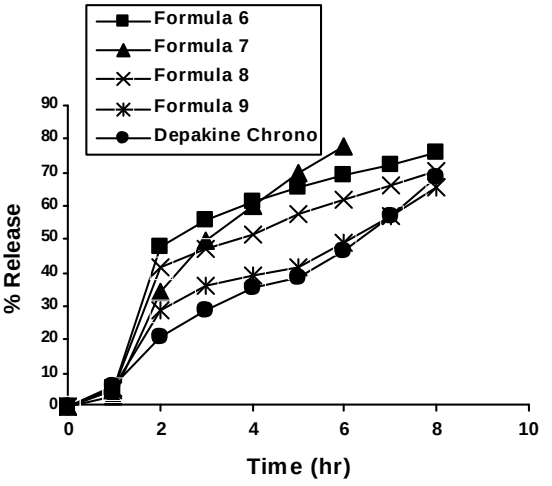

Fig. 2: Effect of different binders on the release profile of SV from Valdisoval coated tablets in 0.1 N HCl for 1 hour followed by phosphate buffer, pH 6.8.

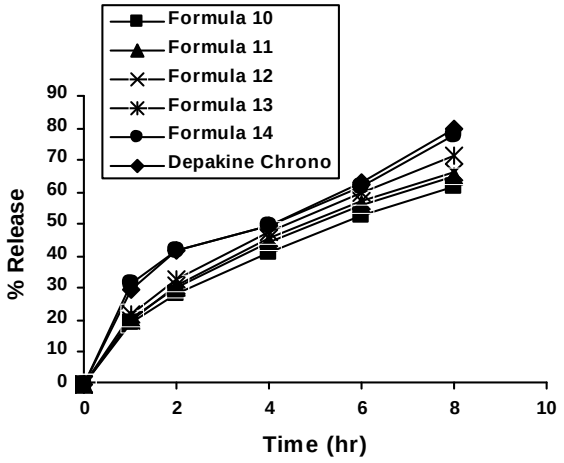

Fig. 3: Effect of hydroxy ethyl cellulose concentration on the release profile of SV from Valdisoval core tablets in phosphate buffer, pH 6.8.

dissolution media was 0.1 N HCl for the first hour followed by phosphate buffer at pH 6.8 for seven more hours. With this enteric film coat, the tablets released about 5.0% of SV in the acid media (first hour). The tablet coat dissolved after changing the dissolution media to phosphate buffer, pH 6.8 and the SV release was controlled by the tablet core matrix formulation. The effect of different binders on the release rate of SV is also shown in Figure 2. Using water as the granulating agent yields tablets with a fast release with a $T_{50\%}$ of approximately 140 minutes (formula 6). When hydroxyl propyl methyl cellulose (HPMC) at 10% w/w concentration was used with ethyl cellulose as a controlled-release polymer mixture, there was a further retardation in SV release ($T_{50\%} \cong 185$ minutes). This mixture of polymers used to control the release of Propranolol HCl.[15] A combination of HPMC and EC was also used to develop a CR matrix tablets containing water-soluble drugs; diphenhydramine HCl and Naproxen sodium.[16]

Eudragit NE-30 D is neutral methacrylic acid ester water dispersion. It is used for granulation processes in the manufacture of sustained release matrix tablets. It was used as a binder at low concentration (solids content 3.0%) with ethyl cellulose (formula 8 and 9). The release of SV was further delayed, but was still away from the innovator products, Figure 2. By increasing the concentration of ethyl cellulose to 25% w/w in the presence of Eudragit NE 30D (formula 9), a release profile closer to that of the brand product was obtained ($T_{50\%}$ = 285 min for the innovator product and 275 min for this proposed formula). Although formula 9 has a closer $T_{50\%}$ values for the brand product, still there are some points in the release profile varied by more than 10%.

The effect of HEC concentration on the release pattern of Valdisoval core tablets is shown in Figure 3. The results showed that there is an inverse relationship between the release of SV and the polymer concentration. This is may be explained by the network structure theory of cellulose ethers during swelling as follows[17]: upon contact with water, tablets containing cellulose ethers start to swell, forming a gel layer around the dry core. On swelling, drug molecules dissolve in the dissolution media and are released by diffusion. Increasing the polymer concentration

increases the number of entanglements per chain in the polymer network that forms during swelling. This decreases the diffusional spaces, hence decreases the drug release by diffusion. The release profile of formulations 10 through 14 was studied in phosphate buffer pH 6.8 dissolution media and was compared to that of the marketed product under the same conditions. At 12.5% w/w HEC concentration (formula 14), the release profile of SV from Valdisoval tablets was almost identical to that of the brand sample. Tablets from this formula were film coated using the formula shown in table 4. The release of these tablets was then tested using 0.1 N HCl dissolution media for 1 hour followed by phosphate buffer, pH 6.8 for another 7 hours and compared with that of the brand name product. The results are shown in Figure 4. The dissolution data was computed according to equation 1 (Table 6). The exponent n was found to approach one, indicating a zero order release mechanism.

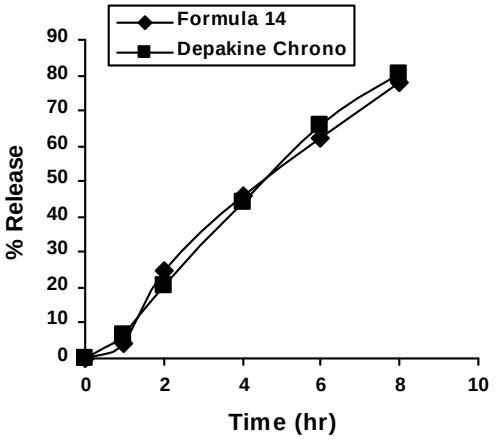

Fig. 4: Release profile of Valdisoval coated tablets (fformula 14) and depakine chrono in 0.1 N HCl for one hour followed by phosphate buffer, pH 6.8.

Table 6: Release rate parameters calculated according to equation 1 for coated tablets from formula 14 and depakine chrono.

Parameter	Formula 14	Depakine Chrono
n	1.0976	0.9577
K (% hr^{-n})	9.535	9.521
R (Correlation coefficient)	0.9993	0.9980

CONCLUSION

Controlled-release Valdisoval tablets were formulated using Eudragits RSPO and RLPO as directly compressible matrix system and using ethyl cellulose with different binders or hydroxy ethyl cellulose by a wet granulation technique. Tablets formulated using 12.5% HEC and then film coated by a solution of Eudragit L100-55 showed a suitable drug release that appears to follow zero order kinetics. Stability study will be conducted later on to elucidate the effect of moisture on the physical properties and the drug content of the prepared tablets.

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