Faculty of Health Sciences, Oslo and Akershus University College of Applied Sciences, Norway

Altered drug release from Orfiril® long following ethanol consumption – extent and consequences

E. Hagesaether

Received June 2, 2017, accepted August 11, 2017

Ellen Hagesaether, Oslo and Akershus University College of Applied Sciences, Postboks 4, St. Olavs plass, 0130 Oslo, Norway
ellen.hagesather@hioa.no

Pharmazie 73: 76–79 (2018) *doi: 10.1691.ph.2018.7096*

Orfiril® long is a widely used antiepileptic drug preparation despite being characterized by features associated with susceptibility to ethanol induced changes to drug release. *In vitro* dissolution studies revealed that 30 % ethanol was required in order to cause dose dumping of valproic acid within two hours at pH 1. However, after exposure to only 5 % of ethanol for 45 minutes at pH 1, the subsequent release of sodium valproate increased by ~ 10 % for the first two hours in ethanol-free media of pH 6.8. The drug solubility increases with pH, likely to also increase the vulnerability to ethanol. This indicates that Orfiril® long is affected by exposure to low concentrations of ethanol as well, only that this effect was exclusively displayed at an elevated pH value not part of the standard regulatory recommendations. Even so, simplified pharmacokinetic simulations revealed no risk of a lower therapeutic effect. Postponing the drug intake in case of moderate drinking, likely to increase the risk of omission altogether, is therefore not necessary. However, for slim patients with a small volume of distribution and low tolerability, a longer duration of mild side effects such as drowsiness and nausea might be experienced.

1. Introduction

Epilepsy is a serious condition affecting at least 65 million people around the world (Ngugi et al. 2010). The condition is characterized by an increased propensity for uncomfortable and dangerous seizures. Therefore, a life-long treatment with antiepileptic drugs is required for most patients.

Valproate belongs to the older generation of antiepileptic drugs, and is widely used (Landmark et al. 2011). The prescribers can chose from various formulations, including prolonged release coated granules marketed as Orfiril® long (Episenta® in the UK), which is administered once or twice daily. The granules are easier to swallow than monolithic formulations, and also allow for flexible dosing. From a biopharmaceutically point of view, granules are known to transit through the gastrointestinal tract in a more reproducible way, hence also reduce the pharmacokinetic variability stemming from the absorption (Stefan 2006). The last point is especially important for antiepileptic drugs of the older generation, where the safety limit between therapeutic and toxic serum concentrations is small (Johannessen and Landmark 2008). Small fluctuations in the serum concentration can then increase the likelihood of seizures in case of low concentrations or experiencing side effects in case of high concentrations.

However, it is known that prolonged release formulations can change their release characteristics in the presence of ethanol. Awareness around this was particularly caused by the product Palladone® SR capsules (FDA Alert 2005), containing coated granules. In vitro dissolution testing revealed accelerated release of the drug hydromorphone when exposed to ethanol. Within 30 min, the drug release increased almost linearly from ~5 % (no ethanol) to ~63 % (20 % ethanol), with a further increase to ~76 % (40 % ethanol). C_{max} values in vivo increased accordingly, and was on average almost doubled in the case of 20 % ethanol and increased by a factor of 5,5 in the case of 40 % ethanol. No effect on the average C_{max} values was seen in the case of 4 % ethanol, although one subject experienced a ~2-fold increase (Walden et al. 2007).

Based on these results the FDA concluded that co-ingestion of Palladone® with alcohol compromises the formulation, causing possibly lethally high peak plasma concentrations of hydromorphone. The FDA further argued that this was likely to be unintentional from the patient`s point of view, as the volume of alcohol necessary to produce dose dumping was within a reasonable range for an alcohol drinker (120 mL of 40% ethanol) (Rappaport 2009). As a consequence, Palladone® was suspended from the market in 2005 (FDA Alert 2005).

According to Jedinger et al. (2014), the coating excipients, i.e. the water insoluble ethyl cellulose and dibutyl sebacate, which are both soluble in ethanol, may have been the reason behind the major effect of ethanol on the drug release characteristics of Palladone® SR capsules. Another contributing factor may be the high total surface area that is exposed to ethanol in case of coated granules.

In the aftermath, the FDA issued recommendations to be used when information of *in vitro* dose dumping in the presence of alcohol was requested. The suggested medium consists of 01 N HCl, with the argument that most of the ethanol is absorbed through the gastric mucosa. The recommended ethanol concentrations (v/v) are 0 %, 5 %, 20 % and 40 %, simulating the consumption of beer, mixed drinks and neat liquor, respectively. The suggested testing time is 2 hours Anand et al. (2011). Lately, the most extensive conditions have been questioned by Rubbens et al. (2016), who presented data pointing to a rapid dilution and absorption of ethanol *in vivo*.

Testing protocols introducing more varied and physiological alternatives have also been followed. Different commercially available formulations of mesalazine were exposed to 0.1 M HCl with 5-40 % ethanol for 0.5-2 h. The release of drug was subsequently followed in acid and at pH 6.8 and 7.4 for 6 h (Fadda et al. 2008). High concentrations of ethanol accelerated the release of mesalazine. The release of mesalazine was faster in acid than in neutral pH, though, probably reflecting the higher solubility of the drug in acid. In contrast to Palladone®, the release was reported not to be affected by concentrations of ethanol as low as 5 %.

Although, for various reasons, epileptic patients are discouraged to drink alcohol, this may not be a realistic expectation for all patients, due to the life-long condition. It is therefore of concern that Orfiril® long also consists of granules coated with the polymer ethyl cellulose, just like the hydromorphone and mesalazine formulations, hinting at a drug release possibly susceptible to ethanol induced changes. Palladone® SR capsules and Orfiril® long also share the same plasticizer: dibutyl sebacate, as well as the excipient ammonio methacrylate copolymer type B, which will gel in contact with water, and allow drug diffusion. But in contrast to hydromorphone and mesalazine, of which the solubility increases in acid, the drug in Orfiril® long, sodium valproate is a slightly soluble acid. However, with a pKa value of 4,8, sodium valproate is 99 % converted to the very soluble sodium valproate at pH 6.8.

The objective of this paper was to investigate the extent and consequences of altered drug release characteristics of Orfiril® long in media of pH 1 and 6.8 due to ethanol consumption. The FDA recommendations for ethanol concentrations and exposure times were consulted. Additionally, special emphasis was placed on simulating moderate drinking. To test whether one beer or two glasses of wine will affect the drug release of the evening dose, the samples were briefly exposed to low concentrations of ethanol in pH 1, and *thereafter* the drug release was followed for several hours in ethanol-free phosphate buffer pH 6.8. To continue the testing at pH 6.8 was considered particularly important for this type of drug: a slightly soluble acid with increased solubility at elevated pH. Furthermore, the feasible approach of using the dissolution results as input data to calculate the changes in the plasma concentrations caused by the ethanol induced altered drug release was used. Hence clinically relevant data was gained without having to perform ethically questionable clinical studies. The overall aim was to be able to better advise epileptic patients on whether to postpone the drug intake in case of moderate drinking, with the risk of omission all together, or if this is not necessary. To the author`s knowledge, the effect of ethanol on anti-epileptic drug formulations has not been reported before.

2. Investigations, results and discussion

2.1. Release of valproic acid in media with pH 1

The *in vitro* release of valproic acid into pH 1 with different concentrations of ethanol is presented in Fig. 1.

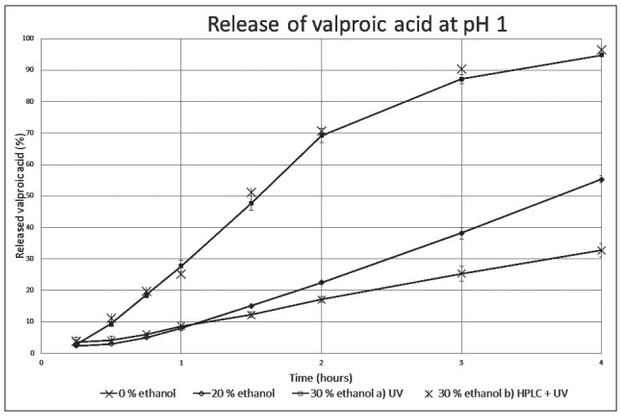

Fig. 1: Effect of ethanol on the dissolution of valproic acid at pH 1. Results are expressed as the mean with the bar showing standard deviations (n=3). Solid fill: significantly different from control samples. No fill: not significantly different from control samples. Additionally, one sample was analyzed with HPLC + UV.

Valproic acid was released slowly into pH 1, with less than 35 % released after 4 h. The release was significantly increased in the presence of ethanol, already after the FDA recommended time limit of 2 h (Anand et al. 2011). Even so, a minimum of 30 % ethanol was required in order to cause dose dumping of valproic acid within 2 h at pH 1. With 40 % ethanol in the dissolution medium, the formulation started to disintegrate. Microscopic examination revealed transparent pellets with less defined edges. This also caused formulation fragments to interfere with the UV measurements.

One sample exposed to 30 % ethanol at pH 1 was additionally analyzed using HPLC + UV, and the results are presented in Fig. 1. Although the results were not superimposable, the HPLC procedure did not cause deviations outside the 95 % confidence interval of the UV results. Additionally, the chromatograms produced by standard and test samples were compared. The retention time of valproic acid was 35-36 min in both cases, and the test samples revealed no additional peaks within the 1 h run time. This indicates that the faster and more environmentally friendly method of UV measurements directly on samples, can be used as an appropriate analytical method, providing the concentration of ethanol is not high enough to cause disintegration of the formulation.

The release enhancing effect of ethanol is not surprising, as Orfiril® long is associated with susceptible characteristics like a large total surface area and excipients recognizable from Palladone® SR. Leakage of ethanol soluble plasticizer has also been suspected of accelerating the drug release from Salofalk® tablets, and ethyl cellulose coated Pentasa® granules were very vulnerable to ethanol (Fadda et al. 2008).

However, the effect of ethanol on the release from Orfiril® long was much smaller than the effects reported on Palladone® SR, where for example ~63 % of the drug hydromorphone was released in only 30 min in the presence of 20 % ethanol (Walden et al. 2007). The explanation may be found in the properties of the drug molecules. Hydromorphone is a base, and the charge acquired at pH 1 will increase the solubility of the drug. The situation is the opposite for the acidic drug valproic acid, where the solubility at pH 1 is only 1.3 mg/mL according to pubchem, even compromising the sink conditions during the experiments. This indicates that the release of highly soluble drugs may be more vulnerable to ethanol. This is an interesting finding in view of the discussion raised by Roberts et al. (2007), where two different mechanisms on how ethanol can increase drug release were presented: either by changing the structure of the excipients responsible for prolonging the release, or by increasing the solubility of the drug. Our findings indicate that the first mechanism probably dominates for Orfiril® long, even though the solubility of valproic acid increases in alcohol according to pubchem.

An ethanol concentration of 30 % were capable of causing dose dumping of Orfiril® long at pH 1. However, 1/3 bottle of spirit or fortified wine must be consumed in only 5 min in order to produce these ethanol concentration in the stomach, respectively (Walden et al. 2007). It is therefore highly unlikely that the formulations will encounter these conditions regularly.

2.2. Release of sodium valproate in media with pH 6.8

Therefore, a second experiment was set up to fulfill three purposes: 1) To take into account a more realistic drinking behavior, represented by either one beer or two glasses of wine. 2) To study the effect of ethanol on the drug release characteristics of Orfiril® long throughout the entire duration time. 3) To gain further insight into the impact of drug solubility on the vulnerability to ethanol induced changes to drug release. This was achieved using a 3 step approach. The ethanol concentrations and exposure times chosen for step 1 and 2 refer to a recently published paper (Rubbens et al. 2016), where the concentrations of ethanol in the stomach and duodenum of 5 fasting volunteers were measured directly, after consumption (within 10 minutes) of alcoholic beverages. The maximum ethanol concentration measured in the stomach was ~4 % after the consumption of 500 ml of beer and ~7 % after the consumption of 200 ml of wine. The average maximum values were 4 % following both beer and wine consumption. After 50 min, the concentrations were less than 2 % and after 100 min almost 0 % following a linear decrease. At the same time points,

the concentrations measured in the duodenum was about half of the concentrations in the stomach. Based on this new knowledge from *in vivo* studies, a 2 hours testing time under acidic conditions with stationary ethanol concentrations, seems excessive. Hence, the shorter exposure times and relatively low ethanol concentrations that the formulation encountered during step 1 (pH 1) was chosen in order to represent the stomach and step 2 (pH 6.8) to represent the duodenum after moderate drinking. Finally, during step 3, the subsequent release of very soluble sodium valproate was measured for 7 hours in ethanol-free medium pH 6.8. Step 3 represented the small intestine after the ethanol has been absorbed. The results from step 3 are compiled in Fig. 2.

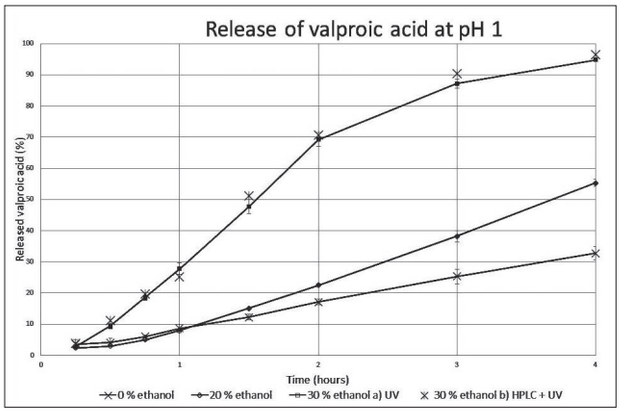

Fig. 2: Effect of ethanol exposure on the subsequent dissolution of sodium valproate in ethanol-free media pH 6.8. Results are expressed as the mean with the bar showing standard deviations (n=3). Solid fill: significantly different from control samples. No fill: not significantly different from control samples. Additionally, the results for one sample was confirmed with HPLC + UV.

The dissolution curves presented in Fig. 2 contain some interesting features. First, the drug release was completed within 7 h, complying with the posology of Orfiril® long, which may be twice a day. Sodium valproate, to which 99 % of valproic acid is converted at pH 6.8, was released faster than the corresponding valproic acid at pH 1, illustrating the effect of solubility on drug release. Secondly, Fig. 2 shows that just a brief exposure to low concentrations of ethanol at pH 1 accelerated the subsequent release of sodium valproate at pH 6.8. The drug release was slightly, yet statistically significantly, higher after exposure to both 5 % and 10 % of ethanol compared to the control samples starting from 0.5 h and continuing for the next 1.5 h. In contrast, neither the immediate nor subsequent release of mesalazine from Pentasa® granules was influenced by 5 % ethanol in the dissolution media (Fadda et al. 2008). While sodium valproate is very soluble, the solubility of mesalazine is limited to a maximum of ~10 mg/ml at pH 1 and decreases to about half this value at pH 6.8. This supports the hypothesis that formulations containing freely soluble drug molecules are more vulnerable to ethanol induced changes to drug release, presented earlier. After 3 h at pH 6.8, the effect of briefly exposing Orfiril® long to ethanol at pH 1, diminished. This indicates that ethanol caused a burst release of sodium valproate, but that any ethanol induced changes to the structure of the coating was reversible. Maybe polymer restructuring led to a subsequent closing of the pores within 3 h. The effect of ethanol was the same in this concentration range of 5-10 %.

Dissolution testing of modified release oral dosage forms involves documenting the release at at least 3 time points, representing ~25 %, 50 % and > 85 % drug release (EMA/492713/2012). After 1 h, the release of sodium valproate from Orfiril® long control samples was about 22 %. Normally, the permitted range in release at any given time point should not exceed a total numerical difference of ±10 % of the labelled content of active substance (EMA/492713/2012). When samples of Orfiril® long were exposed to 10 % ethanol during step 1, about 30 % of the sodium valproate was subsequently released within the first hour at pH 6.8. The product may therefore fail the pharmacopoeia test.

2.3. Simulation of plasma concentrations

Alterations to the plasma concentrations will be the real indication of any clinical consequences. However, pharmacokinetic studies examining whether there is an alcohol-formulation interaction *in vivo* is not recommended as a routine due to the associated risks imposed on the study subjects (Meyer and Hussain 2005). Therefore, *in vivo* plasma concentrations of sodium valproate were predicted from the *in vitro* dissolution data of Orfiril® long using calculations based on the convolution technique (Qureshi 2010). The simulations were made for two types of patients: a normaly sized patient with an average V_D, and a slim patient with a low V_D. Both patients used Orfiril® long modified release granules 1000 mg two times daily, morning and evening, administered with a 12 h interval. The effect of administering the evening dose with two glasses of wine is illustrated in Fig. 3.

According to Fig. 3, the clinical effect of administering Orfiril® long with even two glasses of wine, is small. The efficacy is actually most likely improved, based on the lower C_{max} values and shorter times with low serum concentration. For example, the

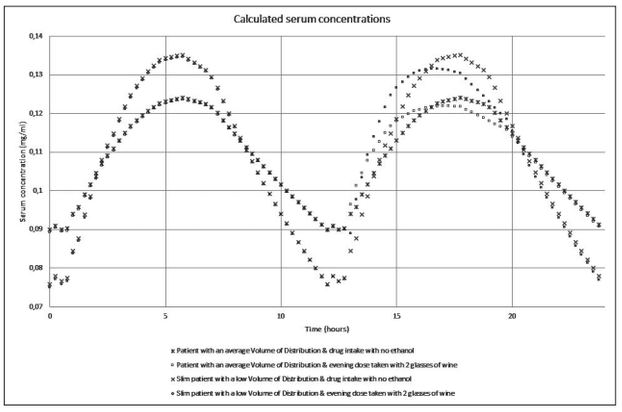

Fig. 3: Predicted serum concentrations based on the dissolution without ethanol (control samples) and dissolution of samples exposed to 10 % ethanol in step 1, representing drug administration with 2 glasses of wine.

serum concentration will reach 0.11 mg/ml 2 h after intake with ethanol, while 2.75 h are necessary to reach the same concentration without ethanol. Low V_D will accentuate the consequences of altered drug release. In this case, a serum concentration of 0.12 mg/ml is reached already after 2.5 h vs. 3.25 h in the case of no ethanol. Assuming the patient has a very low tolerability, a longer duration of mild side effects such as drowsiness and nausea might then occur.

2.4. Conclusions

An ethanol concentration of 30 % was required in order to cause dose dumping of valproic acid from Orfiril® long modified release granules in media of pH 1. On the other hand, just brief exposure to low concentrations (5 %) of ethanol caused a slight, yet statistically significant, increase in the subsequent release of sodium valproate in ethanol-free media of pH 6.8. Put together, is seems like ethanol`s ability to increase the permeability of the very soluble sodium valproate was more pronounced than ethanol`s ability to increase the solubility of the slightly soluble valproic acid. In other words, ethanol exerted the most effect on the formulation, and the effect exerted on the solubility of the drug molecules was of less importance, in this case. Hence, the regulatory focus on pH 1 might not detect the total effect of ethanol on this particular product. However, whether this is the case for all prolonged release formulations containing a slightly soluble acid still remains to be confirmed.

Clinical implications of ethanol induced changes to drug release can be avoided by postponing the drug intake until 3 hours after the ingestion of ethanol (Walden et al. 2007). However, this strategy

Table1: The design/Design of the in vitro dissolution testing, conducted at pH 1 and pH 6.8. The drug release testing at pH 6.8 was inspired by (Fadda et al.,2008) in using 3 steps, where the granule samples were briefly exposed to low concentrations of ethanol in step 1 and 2 and thereafter the drug release was followed for several hours in ethanol-free media.

Drug release at pH 1			
Dissolution media: 900 ml 0.1 M HCl pH 1 Residence time: 4 hours			
Experiment no.:	Concentration of ethanol v/v %		
1 (control)	0 %		
2 (as recommended by FDA)	20 %		
3	30 %		
4 (as recommended by FDA)	40 %		
Drug release at pH 6.8			
Step 1: Dissolution media: 900 ml 0.1 M HCl pH 1	Residence time: 45 minutes		
Step 2: Dissolution media: 1 L phosphate buffer pH 6.8	Residence time: 5 minutes		
Step 3: Dissolution media: 1 L phosphate buffer pH 6.8	Residence time: 7 hours		
Experiment no.:	Concentration of ethanol v/v %		
1 (control)	*Step 1*: 0 %	*Step 2*: 0 %	*Step 3*: 0 %
2 (representing intake of granules together with one beer)	*Step 1*: 5 %	*Step 2*: 3 %	*Step 3*: 0 %
3 (representing intake of granules together with 2 glasses of wine)	*Step 1*: 10 %	*Step 2*: 5 %	*Step 3*: 0 %

may increase the risk of memory slips leading to omission of the dosage altogether. Predictions of the fluctuations inflicted to the plasma concentrations revealed that no such recommendations are necessary for Orfiril® long, and that a normaly sized patient can administer the dose without precautions even after the consumption of two glasses of wine.

3. Experimental

3.1. Materials

The manufacturer of Orfiril® long modified release granules 1000 mg was Desitin Arzneimittel GmbH, and the tested batch no. was 14003579. Valproic acid sodium salt (batch no. MKBS2723V) was purchased from Sigma-Aldrich.

Two types of dissolution media were used: 1) 0.1 M HCl, pH 1, and 2) phosphate buffer pH 6.8. 0.1 M HCl was prepared from HCl fuming 37 % (12 M) purchased from Merck, and purified water. The buffer solution was prepared by diluting Ph. Eur. phosphate buffer solution pH 6.8 R1 a 100 times in purified water. The Ph. Eur. phosphate buffer R1 consisted of potassium dihydrogen phosphate and disodium hydrogen phosphate, both from Merck, in purified water. Rectified ethanol from Kemetyl was added to prepare the required ethanol concentrations (Table 1).

The mobile phase for HPLC consisted of 50 % methanol pro analysis, from Merck, and 50 % Ph. Eur. phosphate buffer pH 3.2. The Ph. Eur. phosphate buffer pH 3.2 was prepared from sodium dihydrogen phosphate monohydrate and ortho-phosphoric acid 85 %, both from Merck, in purified water.

3.2. Methods

In vitro dissolution testing was conducted using a basket apparatus (100 rpm, 37 °C) from Erweka complying with the specifications in Ph. Eur. Drug release in media with pH 1 was tested using four different experiments. In pH 6.8, 3 different experiments were carried out. The complete design with brief explanations is presented in the Table. Three granules were tested for each type of experiment.

Samples were taken from the vessels after 15, 30, 45 min and after 1, 1.5, 2, 3, 4, 5 and 7 h. The original pH values were confirmed in the vessels at the end of the experiments.

The main analytical method for determining the amounts of dissolved valproic acid (at pH 1) and sodium valproate (at pH 6.8) was UV (Ultrospec 1100 pro, Amersham) at the absorption maximum of λ=210 nm. The suitability of this method was confirmed using HPLC + UV (D680 pump, ASI-100 automated sample injector, UVD 1700, all from Dionex) using an Ultra C18 5 µm column (Rtx®-5, serial 505434 from Restek International) on selected samples. The run time was 1 hour per sample, the mobile phase consisted of 50:50 methanol:phosphate buffer 3.2, the flow rate was 1.0 ml/min, temperature 25 °C, sample volume 100 µl and λ 210 nm.

Data are presented as the average and standard deviations of the three formulations tested in parallel, unless otherwise stated. Statistically significant differences are discussed at $p < 0.05$ using the student`s t-Test (heteroscedastic, two tailed distribution).

The results from the *in vitro* dissolution experiment no. 1 and 3 (see Table), at pH 6.8, were used as input data for simulating plasma concentration curves using the convolution method using a spread-sheet software (Qureshi 2010). The amount of drug going into the blood serum and the amount being cleared from the blood serum, following the administration of 1000 mg prolonged release granules two times daily (with intervals of 12 h), were calculated per 15 min. The concentration curves obtained from drug intake without ethanol (experiment no. 1) were compared to the simulated situation of taking the evening dose with two glasses of wine (experiment no. 3). The dissolution data from step 1 were taken from the drug release at pH 1. Missing experimental dissolution data from step 3 were extracted from the linear curve (R^2> 0,99) of drug released vs. time. The pharmacokinetic parameters necessary to conduct the calculations were found in the SPC of Orfiril® long: the absorption of valproic acid and sodium valproate is fast and complete, the plasma clearance is 12.7 ml/min for patient suffering from epilepsy, the volume of distribution (V_D) is 0.13-0.23 L/kg. Two types of patients were used in the simulations: a) a normaly sized patient (70 kg) with an average V_D of 0.18 L/kg and b) a slim patient (55 kg) with a small V_D (0.13 L/kg).

Acknowledgments: The author would like to thank May Nha Tran Nguyen, Hutsuda Lawrence, Kathrine Martenstangen, Fartun Hussain Ali, Sabrin Moueffaq, Anushik Safaryan, Ikram Massoudy and Thanh Van Le for their contribution in carrying out the dissolution experiments and Elisabeth Henrohn for technical support with HPLC.

Conflicts of interest: None declared.

References

Anand O, Lawrence XY, Conner DP, Davit BM (2011) Dissolution testing for generic drugs: an FDA perspective. AAPS J 13: 328-335.

EMA/492713/2012 Guideline on quality of oral modified release products. European Medicines Agency.

Fadda HM, Mohamed MA, Basit AW (2008) Impairment of the in vitro drug release behaviour of oral modified release preparations in the presence of alcohol. Int J Pharm 360: 171-176.

FDA Alert (2005) Information for Healthcare Professionals: Hydromorphone Hydrochloride Extended-Release Capsules (marketed as Palladone). 7/2005:

Jedinger N, Khinast J, Roblegg E (2014) The design of controlled-release formulations resistant to alcohol-induced dose dumping–A review. Eur J Pharm Biopharm 87: 217-226.

Johannessen SI, Landmark CJ (2008) Value of therapeutic drug monitoring in epilepsy. Expert Rev Neurother 8: 929-939.

Landmark CJ, Fossmark H, Larsson PG, Rytter E, Johannessen SI (2011) Prescription patterns of antiepileptic drugs in patients with epilepsy in a nation-wide population. Epilepsy Res 95: 51-59.

Meyer RJ, Hussain AS (2005) Awareness topic: mitigating the risks of ethanol-induced dose dumping from oral sustained/controlled release dosage forms. FDA's ACPS Meeting

Ngugi AK, Bottomley C, Kleinschmidt I, Sander JW, Newton CR (2010) Estimation of the burden of active and life time epilepsy: a meta analytic approach. Epilepsia 51: 883-890.

Qureshi SA (2010) In vitro-in vivo correlation (ivivc) and determining drug concentrations in blood from dissolution testing–a simple and practical approach. Open Drug Deliv J 4: 38-47

Rappaport BA (2009) Memorandum: Hydromorphone extended release (HMER) regulatory history. FDA Center for Drug Evaluation and Research

Roberts M, Cespi M, Ford JL, Dyas AM, Downing J, Martini LG, Crowley PJ (2007) Influence of ethanol on aspirin release from hypromellose matrices. Int J Pharm 332: 31-37.

Rubbens J, Brouwers J, Wolfs K, Adams E, Tack J, Augustijns P (2016) Ethanol concentrations in the human gastrointestinal tract after intake of alcoholic beverages. Eur J Pharm Sci 86: 91-95.

Stefan H (2006) Sustained Release Valproate in the Treatment of Epilepsy. Neuronews 6: 1-8.

Walden M, Nicholls FA, Smith KJ, Tucker GT (2007) The effect of ethanol on the release of opioids from oral prolonged-release preparations. Drug Dev Ind Pham 33: 1101-1111.