Available online at www.sciencedirect.com
ScienceDirect
International Journal of Pharmaceutics 350 (2008) 65–69
INTERNATIONAL JOURNAL OF PHARMACEUTICS
www.elsevier.com/locate/ijpharm

Comparison of the stability of split and intact gabapentin tablets☆

Donna A. Volpe[a], Abhay Gupta[a], Anthony B. Ciavarella[a], Patrick J. Faustino[a], Vilayat A. Sayeed[b], Mansoor A. Khan[a,*]

[a] *Division of Product Quality Research, Office of Pharmaceutical Science, Food and Drug Administration, Life Science Building 64, 10903 New Hampshire Avenue, Silver Spring, MD 20993, USA*
[b] *Office of Generic Drugs, Office of Pharmaceutical Science, Food and Drug Administration, 7500 Standish Place, Rockville, MD 20855, USA*

Received 5 July 2007; received in revised form 26 July 2007; accepted 16 August 2007
Available online 31 August 2007

Abstract

The purpose of this study was to determine the stability differences between split and intact gabapentin tablets. Gabapentin tablets from three different manufacturers (G1, G2 and G3) were tested for a period of 9 weeks under long-term (25 °C/60% RH) and intermediate stability (30 °C/60% RH) storage conditions after storage in closed amber pharmacy dispensing containers. Samples were analyzed for dissolution and potency using validated HPLC methods. Potency test also included the quantitation of gabapentin's main degradation product. Tablets from all manufacturers and at all time points had potency >90%. At 9 weeks, a statistically significant decrease ($p < 0.02$) in gabapentin potency was observed for the whole and split G2 and G3 tablets under the intermediate storage conditions. At the end of 9 weeks, all samples also showed slightly higher levels of degradation product which was statistically significant ($p < 0.01$) for samples stored under intermediate stability storage conditions and exceeded the proposed USP (PF, 2006) limit for the G3 split and intact tablets. No difference was observed between the potency and dissolution of the intact and the split tablets from the same manufacturer and the three products tested remained stable throughout the study period. The results suggest that splitting of gabapentin tablets did not affect the stability of these particular drug products tested as part of this study when stored under normal storage conditions for a period of up to 9 weeks. However, the results should not be extrapolated to other gabapentin drug products and to other tablet dosage forms.

Keywords: Split-tablet; Stability; Gabapentin

1. Introduction

Tablets are often split by consumers to divide a dose into smaller amounts to meet individual needs, to better titrate dosage requirements or for cost reasons. The drugs recommended for splitting by insurance companies for cost reasons include atorvastatin, citalopram, gabapentin, olanzapine and sertraline tablets. The testing by the drug product manufacturers ensures the stability of the whole tablets that have not been altered following manufacturing. However, they do not test, nor are required by the FDA to study the stability of different drug products in the split form. The concern of some professionals is that the stability and quality of these split tablets may not be the same as the intact product. This is especially true if the split tablets are stored for a period of time by the patient.

Since tablet splitting exposes the core of the tablet to the environment, the split tablets may not have the same stability profile as determined by the manufacturer for intact tablets. Tablets split by a patient or pharmacist and returned to the bottle may be subject to increased friability and fragmentation, a change in dissolution (because of change in surface area) and enhanced degradation (because of change in exposure to air, moisture, or light). There is insufficient scientific data or reports on the quality of cut tablets when stored for a period of time.

Weight variation is the most commonly cited problem when the tablets are split. McDevitt et al. (1998) reported the variability of manually splitting hydrochlorothiazide 25 mg tablets by volunteers. Out of the 1752 split portions, more than 40% deviated by >10% of the ideal weight, and more than 12% of the tablets deviated by >20% of the ideal weight. Sim-

☆ These are scientific findings and the views are those of the authors. They do not represent views and/or policies of the agency.

* Corresponding author. Tel.: +1 301 796 0016; fax: +1 301 796 9816.
E-mail address: mansoor.khan@fda.hhs.gov (M.A. Khan).

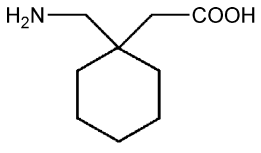
0378-5173/$ – see front matter © 2007 Elsevier B.V. All rights reserved.
doi:10.1016/j.ijpharm.2007.08.041

ilarly Rosenberg et al. (2002) reported weight failures by USP standards for 22 different products with 560 split tablet halves. There was an unacceptable incidence of weight variation with only 7 of the 22 (31.8%) dispensed prescriptions meeting USP standards. In another study, Teng et al. (2002) found significant weight variation with 11 commonly used split tablets and indicated that 8 would fail the USP weight uniformity test if liberally interpreted and applied to the split tablets.

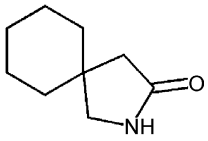
Studies on the effect of tablet splitting on a product's *in vitro* dissolution profile have yielded varying results. For sustained- or extended-release drug products, tablet splitting either had no effect (Skoug et al., 1991; Mandal, 1996) or increased the rate of release of the drug from the split tablet (Erramouspe and Jarvi, 1998; Simons et al., 1982; Shah et al., 1987). Several clinical studies on the effectiveness of statin drugs (atrovastatin, lovastatin, simvastatin) found that tablet splitting did not negatively affect levels of low density lipoproteins, total cholesterol and/or triglycerides in patients (Parra et al., 2005; Duncan et al., 2002).

This study attempts to address these product quality issues and their potential impact on public safety due to the practice of splitting of gabapentin tablets. Gabapentin(1-(aminomethyl)cyclohexaneacetic acid) is a γ-aminobutyric acid (GABA) analog used for the treatment of seizures in adults and children (Walker and Patsalos, 1995). It has also been shown to be effective for neuropathic pain (Finnerup et al., 2002). Gabapentin is widely used due to its relatively mild side-effect profile when compared with older generation antiepileptics (Baillie and Power, 2006). Recent scientific literature proposes that gabapentin achieves its therapeutic effects by blocking calcium channels (Sills, 2006) or mimics the action of GABA on $GABA_B$ receptors.

Gabapentin [structure I] degrades via intramolecular cyclization to form a γ-lactam: 3,3-pentamethylene-4-butyrolactam (2-azaspiro[4,5]decan-3-one) [lactam, structure II].



I



II

The lactam has been shown to cause adverse pharmacological activity in a pre-clinical animal model (Potschka et al., 2000). Due to potentially adverse pharmacological effect of lactam and the presence of gabapentin in the tablet-splitting program of some insurance companies, gabapentin drug products were selected to test the effect of splitting on tablet stability.

2. Materials and methods

2.1. Materials

Gabapentin tablets (600 mg) packed in bulk plastic bottle containers were obtained from three different manufacturers (G1, G2 and G3) and stored at 25 °C and 60% relative humidity (RH). Gabapentin and lactam (USP related compound A) reference standards were purchased from United States Pharmacopeia (USP) (Rockville, MD). Nylon syringe filters were purchased from Sun SRI (Rockwood, TN). HPLC grade monobasic potassium phosphate, ACS grade phosphoric acid, ACS grade dibasic potassium phosphate and HPLC grade acetonitrile and methanol were from Fisher Scientific (Fairlawn, NJ), JT Baker (Philipsburg, NJ), and Burdick and Jackson (Muskegon, MI). HPLC ready 18 mΩ water was obtained from a Milli-Q Gradient A-10 water purification system (Millipore Corp., Bedford, MA).

2.2. Sample preparation

Gabapentin tablets from each manufacturer were split into two parts using a tablet-splitter (Apothecary Products, Inc., Burnsville, MN). Twenty intact tablets and 40 split portions from each manufacturer were weighed to determine the weight variation of the intact and the split tablets. Thirty-four intact tablets and 68 split halves of each product were randomly dispensed into individual amber pharmacy container for each time point and closed using a child resistant cap. Samples were stored in monitored environmental chambers (Hotpack, Philadelphia, PA or Electrotech, Glenside, PA) under long-term storage conditions (25 °C/60% RH) or intermediate stability conditions (30 °C/60% RH) for 9 weeks. On the appropriate time points (0, 2, 4, 6 and 9 weeks), the closed pharmacy vials were removed from the incubators and allowed to equilibrate at room conditions for at least one hour. Samples were then analyzed for potency, hardness and dissolution. Twenty intact tablets or 40 split portions were transferred to a mortar and ground with a pestle to a fine, homogenous powder. Powder obtained from tablet grinding was aliquoted into labeled vials for subsequent potency experiments.

2.3. Potency determination

Gabapentin potency and the lactam concentration were determined using a validated HPLC method (Ciavarella et al., 2007). Briefly, an acetonitrile: 10 mM KH_2PO_4/10 mM K_2HPO_4 (pH 6.2) (8:92, v/v) mobile phase was used on a 250 mm × 4.6 mm 5 μm Brownlee Spheri-5 Cyano column (Perkin-Elmer, Waltham, MA). The compounds were eluted isocratically at a flow rate of 1 mL/min over 10 min and analyzed with UV detection at 210 nm. A portion of the ground tablets equivalent to about 125 mg of gabapentin was accurately weighed and transferred to a 50 mL volumetric flask. Approximately 40 mL of HPLC mobile phase was added to the flask and the contents were sonicated for 15 min followed by 15 min on a mechanical shaker at 100 rpm. The flask was adjusted to volume and mixed well. The resulting solution was filtered using a 0.45 μm nylon filter into standard analytical glass vials and injected into the HPLC. Three samples were prepared from the powder mix of each 20 intact and 40 split tablets according to USP criteria and injected twice. The amount of gabapentin and the lactam were determined by comparing the peak area of the test solutions with those of the standard solutions of the USP gabapentin and lactam reference standards.

The amount of gabapentin was determined using the formula

$$100\left(\frac{C_S}{C_U}\right)\left(\frac{r_U}{r_S}\right)$$

in which C_S and C_U are the concentrations, in mg/mL, of gabapentin in the standard solution and the test sample, respectively; and r_U and r_S are the peak responses obtained from the test sample and the standard solution, respectively.

The amount of gabapentin related compound A was determined using the formula

$$100\left(\frac{C_S}{C_T}\right)\left(\frac{r_U}{r_S}\right)$$

in which C_S is the concentration, in mg/mL, of USP gabapentin related compound A RS in the standard solution; C_T is the concentration, in mg/mL, of gabapentin in the test samples; and r_U and r_S are the individual peak responses for gabapentin related compound A obtained from the test samples and standard solution, respectively.

2.4. Dissolution testing

A calibrated USP II apparatus (Van Kel VK7000, Cary, NC) with paddles at 50 rpm was used for the dissolution experiment with 6 intact or 6 split tablets. The weights of individual intact and split tablets were recorded before the dissolution test to determine the variation in the sample weight due to tablet splitting. The dissolution media was 900 mL of 0.06 N HCl maintained at 37 °C. Five millilitre of media was removed and filtered through a 0.45 μm nylon filter at 15, 30 and 45 min. Samples were diluted 60:40 with a methanol:acetonitrile:250 mM KH_2PO_4 (1:1:6) dilution mix and analyzed using a validated HPLC method (Gupta et al., 2008). Briefly, a methanol:acetonitrile:20 mM KH_2PO_4 (pH 2.2) (5:5:90, v/v) mobile phase was used on a 250 mm × 4.6 mm 5 μm Luna Cyano column (Phenomenex Inc., Torrance, CA). The compounds were eluted isocratically at a flow rate of 1.25 mL/min over 10 min with UV detection at 210 nm. The amount of gabapentin dissolved was determined by comparing the peak area of the test solutions with those of the standard solutions of the USP gabapentin reference standard using the formula

$$\frac{(r_U \times C_S \times 900 \times 100)}{r_S \times LC}$$

in which r_U and r_S are the peak responses for the standard solution and the test samples, respectively; C_S the concentration, in mg/mL, of the standard solution; 900 the volume, in mL, of dissolution medium; 100 the conversion factor to percentage; LC is the tablet label claim in mg (600 for the whole tablets and 300 for the split tablets).

3. Results and discussion

The tablets from the three manufacturers showed a higher variation in the sample weights for the split tablets as compared to the intact tablets. The intact tablets from the three manufacturers had a relative standard deviation (RSD) of <0.8% while the G1, G2 and G3 split tablets showed a significant higher variation with RSDs of 4.0, 6.0 and 5.5%, respectively. The G1 and G3 tablets were scored while the G2 tablets were unscored. The G1 tablets gave an even cut while the G2 and G3 tablets gave uneven cuts and the halves often had "burrs" on the cut edge thus giving higher weight variation for the split portions.

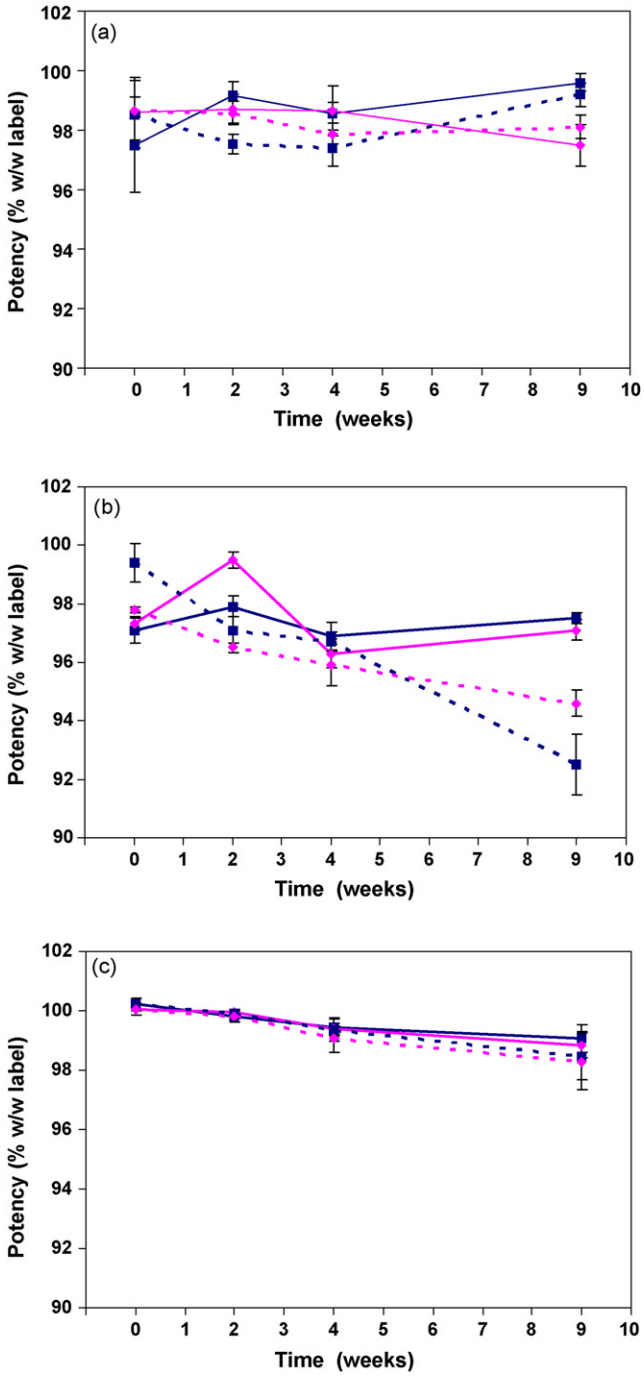


Fig. 1. Change in gabapentin potency for whole (■) and split (♦) drug products (a: G1; b: G2; c: G3) over 9 weeks under 25 °C/60% RH (—) and 30 °C/60% RH (– –) storage conditions.

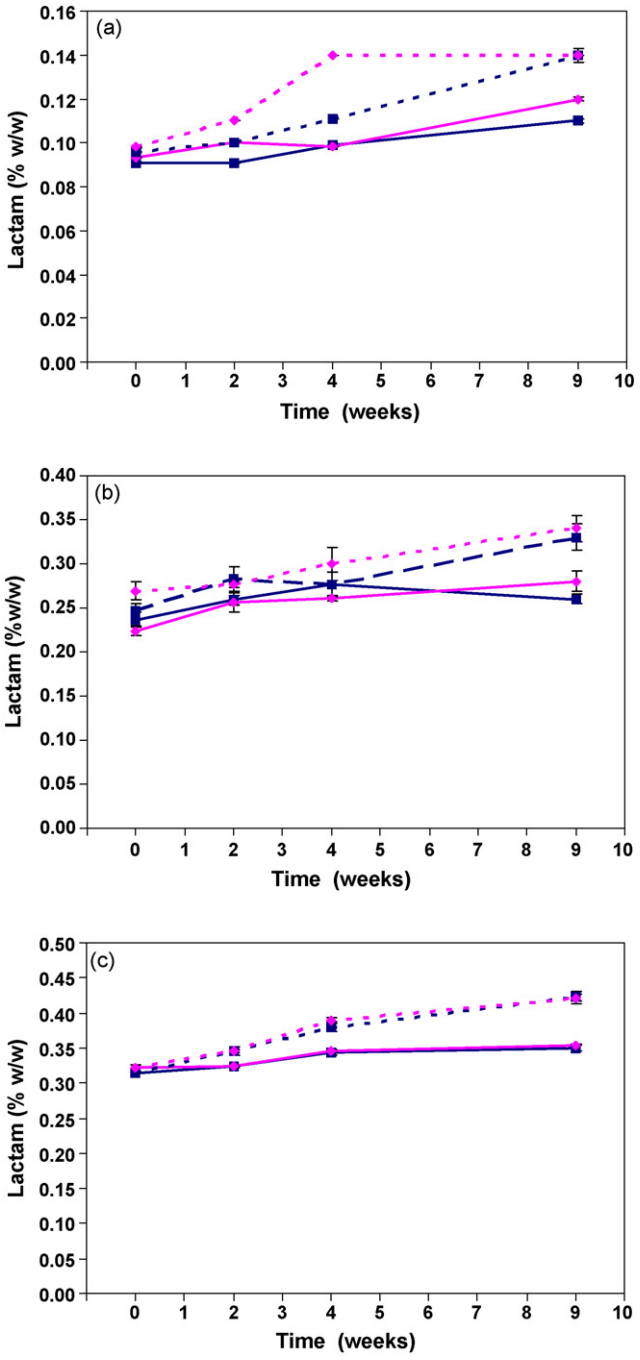


Fig. 2. Change in lactam concentration whole (■) and split (♦) drug products (a: G1; b: G2; c: G3) over 9 weeks under 25 °C/60% RH (—) and 30 °C/60% RH (– –) storage conditions.

Tablets from all manufacturers had potency >90% at all time points. Gabapentin potency of whole and split G1 tablets showed no change during the entire 9-week period, while whole and split G2 and G3 tablets under the intermediate storage conditions showed a significant decrease ($p < 0.02$) in potency at the end of 9 weeks period as compared to the day zero samples (Fig. 1). There were no differences in gabapentin potency-time relationship between the intact and the split tablets from the same manufacturer.

For the three drug products tested, an increase in the amount of lactam was observed for the samples stored under both storage conditions. However, only samples stored under intermediate storage conditions (30°) showed a statistically significant ($p < 0.01$) increase in the lactam concentration (Fig. 2). The whole and the split samples of G3, stored under intermediate storage conditions (30°) for 9 weeks, had lactam concentrations of $0.42 \pm 0.01\%$ and $0.42 \pm 0.01\%$, respectively, which are slightly higher than the proposed limit of 0.4% in the Pharmacopeial Forum 32(6) (2006). At all earlier time points, the lactam levels were, however, within the above proposed PF 32(6) limits. The testing on G3 at the 9 weeks time point was done during the last month of its 24 months expiration period and may be the reason for the elevated levels of the lactam concentration. However, there were no differences in the amount of degradation product measured between the intact and the split tablets from the same manufacturer at all time points and at both temperatures.

The three drug products tested showed some differences within their dissolution profiles (Fig. 3) with G2 displaying a significantly faster ($p < 0.01$ at 10 and 20 min) dissolution than the other two drug products. However, all three tablet products tested showed greater than 97% dissolution in 45 min and satisfied the proposed Pharmacopeial Forum 32(6) (2006) limit of not less than 80% dissolved in 45 min. Since all samples showed almost complete dissolution within 45 min, additional samples beyond it were not tested. No significant differences were observed in the amount of gabapentin dissolved or the dissolution profiles when comparing the intact and the split tablets samples from the same manufacturer stored under either stability condition for the duration of this study. For all samples, the profiles for the whole and the split tablets were found to be identical to one another and to the profiles shown in Fig. 3.

The excipients (fillers, binders, lubricants, etc.) used to formulate a pharmaceutical drug product influences its stability and dissolution characteristics. Due to this reason, all drug products containing the same active pharmaceutical ingredient are required to be bioequivalent to the reference listed drug product, in addition to meeting all pharmacopeial requirements. The three drug products tested as part of this study were obtained

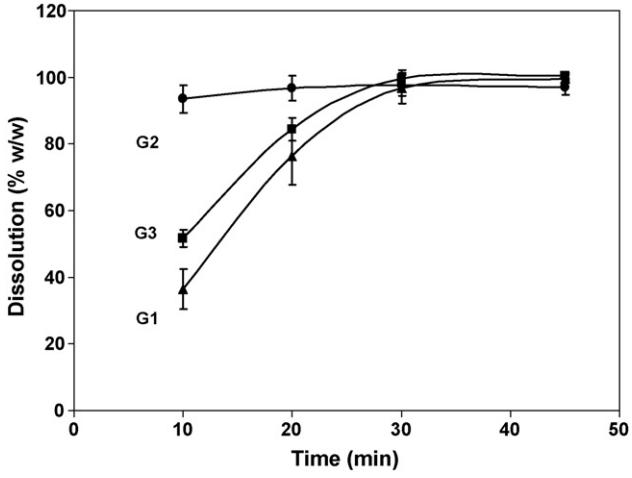


Fig. 3. Dissolution profiles of the three gabapentin drug products.

from three different pharmaceutical manufacturers. The differences observed in the stability and dissolution characteristics of the three products were within the allowed limits, and could be due to the differences in the ingredients used in their respective formulation.

4. Conclusions

The gabapentin drug products tested in this study were found to be stable up to a period of 9 weeks under long-term and intermediate storage conditions as whole and split tablets. No significant differences in product quality were observed for the split tablets as compared to the intact tablets. The potency and dissolution results satisfied the proposed acceptance criteria for the gabapentin tablets in the PF 32(6) (2006). Lactam levels were higher for two of the three drug products tested at all time points but were within the limits of the acceptance criteria proposed in PF 32(6) except for the 9 weeks whole and split samples of G3 stored under intermediate storage condition.

The tablets split in this study were done under strict laboratory conditions. The potential for poor results from tablet splitting (significant split-tablet weight variability) by consumers, especially the elderly, may affect consumer compliance (small or crumbling tablets) and clinical outcome. Tablet weight variability from poor tablet splitting may also result in variations in some pharmacokinetic endpoints and may also involve some increased risk for narrow therapeutic drugs that cannot be fully understood based on the stability assessment for this split tablet study. Therefore the stability results of this study should not be extended to other drug products or in no way conclude that the quality attributes of split tablets are fully understood.

References

Baillie, J.K., Power, I., 2006. The mechanism of action of gabapentin in neuropathic pain. Curr. Opin. Investig. Drugs 7, 33–39.

Ciavarella, A.B., Gupta, A., Sayeed, V.A., Khan, M.A., Faustino, P.J., 2007. Development and application of a validated HPLC method for the determination of gabapentin and its major degradation impurity in drug products. J. Pharm. Biomed. Anal. 43, 1647–1653.

Duncan, M.C., Castle, S.S., Streetman, D.S., 2002. Effect of tablet splitting on serum cholesterol concentrations. Ann. Pharmacother. 36, 205–209.

Erramouspe, J., Jarvi, E.J., 1998. Effect on dissolution from halving methylphenidate extended-release tablets. Ann. Pharmacother. 32, 1372–13723.

Finnerup, N.B., Gottrup, H., Jensen, T.S., 2002. Anticonvulsants in central pain. Expert Opin. Pharmacother. 3, 1411–1420.

Gupta, A., Ciavarella, A.B., Sayeed, V.A., Khan, M.A., Faustino, P.J., 2008. Development and application of a validated HPLC method for the analysis of dissolution samples of gabapentin drug products. J. Pharm. Biomed. Anal. 46, 181–186.

Mandal, T.K., 1996. Effect of tablet integrity on the dissolution rate of sustained-release preparations. J. Clin. Pharm. Ther. 21, 155–157.

McDevitt, J.T., Gurst, A.H., Chen, Y, 1998. Accuracy of tablet splitting. Pharmacotherapy 18, 193–197.

Parra, D., Beckey, N.P., Raval, H.S., Schnacky, K.R., Calabrese, V., Coakley, R.W., Goodhope, R.C., 2005. Effect of splitting simvastatin tablet for control of low-density lipoprotein cholesterol. Am. J. Cardiol. 95, 1481–1483.

Pharmacopeial Forum 32 (2006) 1695–1697.

Potschka, H., Feuerstein, T.J., Loscher, W., 2000. Gabapentin-lactam, a close analogue of the anticonvulsant gabapentin, exerts convulsant activity in amygdala kindled rats. Naunyn Schmiedeberg's Arch. Pharmacol. 361, 200–205.

Rosenberg, J.M., Nathan, J.P., Plakogiannis, F., 2002. Weight variability of pharmacist-dispensed pill tablets. JAPhA 42, 200–205.

Shah, V.P., Yamamoto, L.A., Schuirman, D., Elkins, J., Skelly, J.P., 1987. Analysis of in vitro dissolution of whole vs. half controlled release theophylline tablets. Pharm. Res. 4, 416–419.

Sills, G.J., 2006. The mechanisms of action of gabapentin and pregabalin. Curr. Opin. Pharmacol. 6, 108–113.

Simons, K.J., Frith, E.M., Simons, F.E., 1982. Dissolution and bioavailability studies of whole and halved sustained-release theophylline tablets. J. Pharm. Sci. 71, 505–511.

Skoug, J.W., Borin, M.T., Fleishaker, J.C., Cooper, A.M., 1991. In vitro and in vivo evaluation of whole and half tablets of sustained-release adinazolam mesylate. Pharm. Res. 8, 1482–1488.

Teng, J., Song, C.K., Williams, R.L., Polli, J.E., 2002. Lack of medication dose uniformity in commonly split tablets. JAMA 42, 195–199.

Walker, M.C., Patsalos, P.N., 1995. Clinical pharmacokinetics of new antiepileptic drugs. Pharm. Ther. 67, 351–384.