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RESEARCH PAPER

Evaluation of Pharmaceutical Quality of Phenytoin Sodium Capsules and Tablets from Multinational Markets*

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ABSTRACT

This report presents the results obtained in the above-titled study for the quality of phenytoin sodium tablets and capsules (100 mg) available in the markets of various countries worldwide, especially members of the Official Laboratories and Medicines Control Services (OLMCS) section of FIP. The products were analyzed following a common protocol based on the methodologies described in the European (Ph.Eur.), British (BP), and/or United States Pharmacopeia (USP). Pharmacotechnic tests (uniformity of weight, disintegration), identification, assay, and dissolution of active ingredient were performed by 23 laboratories from 20 countries that submitted data from 52 samples representing 37 products available in the local markets. Innovator products from 17 countries were analyzed in LEF. Most products tested fulfilled the pharmacopeial requirements concerning uniformity of weight, disintegration, identity, and content. Marked differences were recorded in respect of in vitro dissolution behavior. This applies not only to the products of different brands but also among lots of the same brand name produced in different countries.

INTRODUCTION

Phenytoin sodium (diphenin, sodium diphenylhydantoin, soluble phenytoin) is used extensively as an anticonvulsant in the treatment of grand mal and psychomotor seizures (1). Phenytoin sodium is a weak acid with pK_a of 8.3 (25°C) and is soluble in water; however, the solution is partly hydrolyzed to the parent acid, which precipitates and turbidity develops (2). It has been classified as a drug with "high risk potential" with respect to bioavailability problems (3), and the formulation of phenytoin products by different manufacturers has been

*Prepared in collaboration with the study group of the OLMCS of the FIP (see Table 2).
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reported to have pronounced influence on the rate and extent of absorption of the drug (4). Particle size, shape, salt form, dosage form, and product excipients are factors that can modify gastrointestinal absorption (5). The drug has a low therapeutic index and displays saturation kinetics at conventional doses. The problems associated with differences in bioavailability between preparations of phenytoin have been documented in Europe, North America, and Australia (6).

Phenytoin products are manufactured as the sodium salt and free acid. Phenytoin sodium is available as capsules, tablets, and injection, whereas phenytoin acid is available as tablets and suspension.

The aim of this multinational study was to obtain information about the quality of phenytoin sodium formulations (100-mg tablets and capsules) available in the markets of different countries all over the world, especially in the markets of members of the Official Laboratories and Medicines Control Services (OLMCS) section of FIP.

Continuing the successful multinational studies performed under the auspices of the OLMCS (7–9), a proposal to conduct an interlaboratory study of the quality of phenytoin sodium capsules and tablets was first suggested by Laboratório de Estudos Farmacêuticos in Lyon, in September 1992, and was officially accepted in Edinburgh, in May 1993. The study was coordinated by Laboratório de Estudos Farmacêuticos (LEF) in Portugal. The three main objectives for this study were (i) the comparison of the all tablets or capsules existing in each country containing 100 mg of phenytoin sodium; (ii) the study of innovator products available in each country, analyzed in LEF, (iii) the assessment of interlaboratory variability with a standard sample of (OM-Hidantoine, lot 116043).

MATERIAL AND METHODS

The study protocol was drafted by LEF and was officially accepted, after discussion, at the 1993 spring meeting of OLMCS. The protocol was developed based on the procedures described in the European (Ph. Eur.), British (BP), and/or United States Pharmacopeia (USP). The test methods of the protocol are summarized in Table 1.

Procedures

Each participant received a standard sample of phenytoin sodium (100 mg/tablet, lot 116043, OM-Hidantoine, Portugal) to analyze according to the common protocol. It was required that the dissolution apparatus should have been calibrated with USP official prednisone calibrator tablets following the Suitability Test as described in the general chapter "<711> Dissolution" in the USP XXII.

Two lots of each phenytoin sodium product (100-mg capsules and/or tablets, whichever were available in the

Table 1

Protocol Requirements for the Collaborative Study

Test (Reference)	Description
Identification (BP 1988—"Phenytoin Sodium Tablets" or "Phenytoin Sodium Capsules")	Infrared absorption spectrum, precipitation (Ppt) reaction, and sodium reaction
Assay (USP XXII—adapted from "Phenytoin Sodium Injection")	HPLC method
Uniformity of weight (Ph. Eur.—"Compressi," 1990, 478)	Individual weight of 20 units
Disintegration (Ph. Eur.—"Compressi," 1990, 478)	Run for 15 min or 30 min for a set of 6 tablets or 6 capsules, respectively
Dissolution (USP XXII—adapted from "Extended Phenytoin Sodium Capsules")	• Medium: 900 ml of water • Apparatus: 1 (basket) at 50 rpm • Times: 10, 20, 30, 60, 90 min • Quantification by HPLC: Column: packing L1 (RP-18) Mobile phase: methanol/water (55:45) Detection: 254 nm (UV)

respective countries) were purchased from the local market (retail pharmacy or wholesaler) and analyzed according to the protocol. All the participants were also invited to send innovator products available in their countries to LEF for analysis in this laboratory.

Statistical Analysis of Dissolution Data

The statistical methods used were the same when analyzing the results of different products, innovators, or for the assessment of interlaboratory variability. There were two phases in the analysis of dissolution results:

- First, in an exploratory stage, we used cluster analysis to search for relatively homogeneous groups according to their results.
- In a second stage, we performed tests to evaluate if the observed differences were statistically significant.

A certain number of decisions must be made before performing the cluster analysis technique: Which variables will serve as the basis for cluster formation? How will the distance between cases (i.e., dissolution curves) be measured? What criteria will be used for combining cases into clusters?

The initial choice of variables determines the criteria that should identify subgroups. In order to fully characterize the dissolution profile, results from the 10th, 20th, 30th, 60th, 90th, 120th, and 180th min were used. The concepts of distance and similarity are basic to cluster analysis, since cases are grouped on the basis of their "nearness." There are many different definitions of distance between two cases, but in this study we chose the *squared Euclidean distances*, given by the following expression:

$$\text{Distance } (X, Y) = \sum_i (X_i - Y_i)^2$$

where X_i and Y_i represent the time points of dissolution curve X and Y, respectively.

The criteria for combining clusters was *Ward's method*. For each cluster, the means for all variables were calculated. Then for each case the squared Euclidean distance to the cluster means was calculated. These distances were summed for all cases. At each step, the two clusters that merge are those that result in the smallest increase in the overall sum of the squared within cluster distances.

Dendograms were used to show graphically all steps in clustering formation. The choice of reported clusters was reached by visual assessment of the grouped dissolution profiles, before determining whether the differences between clusters were statistically significant.

Means and standard deviations were calculated for each time of dissolution of each cluster. Mean differences were assessed, first, using the multivariate test of T^2 Hotelling to evaluate simultaneous differences between dissolution profiles from the 10th to the 180th minute result between clusters and, secondly, using the Student t test to evaluate the mean differences for each dissolution time. Every time a normal distribution of data was not observed [result given by Kolmogorov–Smirnov test (10)], we used the alternative nonparametric test [Mann–Whitney (10)].

The decision rule for all tests was based on the 5% level of significance.

RESULTS AND DISCUSSION

The participants sent all their results to LEF. Twenty-three laboratories from 20 countries submitted data derived from 52 samples representing 37 different products available in the respective local markets. Innovators from 17 countries were evaluated in the comparative study performed at LEF in Lisbon. Table 2 lists the participating institutions and investigators.

Quality of Phenytoin Sodium Formulations—Comparison

We considered the results for tablets and capsules separately for each of the parameters tested. Details of the products tested are summarized in Tables 3 and 4.

Uniformity of Weight

- *Capsules* from the different countries had a mean weight between 200 and 260 mg, with standard deviations from 1.7% (Germany) to 18.7% (Argentina).
- *Tablets* from the different countries had a large range of weights for the same dose of phenytoin. The tablets from Argentina had a mean weight of 868 mg (AG-T1), and those from China 120 mg (CHI-T2). Standard deviations ranged from 2.2% (Mexico) to 17.0% (China).

Identification

All countries performed the three tests for identification—IR, Na reaction, Ppt reaction—proposed in the

Table 2

Names of the Institutions and Principal Investigators of the Participating Countries

Country	Institution	Investigators
Argentina	Universidad de Buenos Aires, Facultad de Farmacia y Bioquimica, Buenos Aires	C. Bregni
Austria	Institut für Pharmazeutische Technologie der Universität Wien, Vienna	H. Viernstein
Canada	Bureau of Drug Research, HPB, Health and Welfare, Ottawa	I. J. McGilveray S. A. Qureshi
China	National Institute of Control of Pharmaceutical and Biological Products	Yu Ruying
Cyprus	State General Laboratory, Nicosia	M. Aletrari
Finland	Lääkelaboratorio National Agency for Medicines, Helsinki	E. Totterman
Germany	Zentrallaboratorium Deutscher Apotheker, Eschborn	H. Blume S. L. Ali
Greece	Aristotle University of Thessaloniki, School of Pharmacy, Thessaloniki	M. Georgarakls
Italy	Istituto Superiore di Sanitá, Rome	E. C. Signoretti
Luxembourg	Laboratoire National de Santé, Division Chimic Toxicologique et Pharmaceutique, Luxembourg	J. L. Robert
Mexico	Universidad Nacional Autonoma de México, México	H. J. Cook
New Zealand	Institute of Environmental Science & Research Limited, Lower Hutt	R. A. Richardson
Portugal	Laboratório de Estudos Farmacêuticos, Lisbon	A. R. Farinha M. G. Paulo
Singapore	Dept. of Scientific Services & Institute of Science and Forensic Medicine, Singapore	Woo Soo-on
Spain	Ministerio de Sanidad y Consumo, Madrid	A. Velazquez
Sweden	Apotheksbolaget AB, Stockholm	H. Selander M. E. Johansson E. Sjöberg
	Läkemedelsverket Medical Products Agency, Uppsala	J. O. Waltersson
Switzerland	Interkantonale Kontrollstelle für Heilmittel, Bern	S. Steiner
The Netherlands	Control Laboratory for the Dispensing Doctors in the Netherlands (CLANAG)	O. M. van Berkel-Geldof
	Laboratory of the Dutch Pharmacists (LNA)	F. J. van de Vaart O. S. N. M. Smeets
	Dutch National Institute for the Quality Control of Drugs (RIGO)	J. Nienhuis
Turkey	Central Institute of Sanitary Protection, Ankara	T. Burat
United Kingdom	Royal Pharmaceutical Society of Great Britain, Medicines Testing Laboratory, Edinburgh	A. G. Davidson
Uruguay	Direccion National de Sanidad de las Fuerzas Armadas, Laboratorio de Biofarmacia, Montevideo	E. Frugoni

protocol on capsules and tablets. No negative identifications were reported.

Disintegration

- *Capsules*: For capsules the disintegration time ranged from 4 to 30 min except a brand from Argentina that gave a value of 50 min (AG-C3). This batch from Argentina also gave a very low value of percentage dissolved at 30 min.
- *Tablets*: The disintegration times ranged from 3 to 30 min for the different tablets.

Table 3

Products Tested in Capsules

Country	Product Name	Batch No.	Manufacturer	Study Code
Argentine	Epamin	7857063	Parke Davis	AG-C1
	Fenigramon	203	Laboratorio Gerardo Ramon y Cia	AG-C2
	Clerin	PO-979	Laboratorio Lasca, Paraguay	AG-C3
Canada	Dilantin	41117	Parke Davis (Canada)	CDN-C1
	Dilantin	3N106	Parke Davis (Canada)	CDN-C2
Cyprus	Epanutin	3N675	Parke Davis	CYP-C1
Germany	Epanutin	0034053	Parke Davis	D-C1
	Epanutin	0035073	Parke Davis	D-C2
Luxembourg	Epanutin	93B01	Parke Davis	L-C1
	Epanutin	93E03	Parke Davis	L-C2
Mexico	Epamin	810632	Parke Davis (Cia Medicinal)	MEX-C1
	Epamin	801747	Parke Davis (Cia Medicinal)	MEX-C2
New Zealand	Dilantin	1706	Parke Davis	NZ-C1
Singapore	Dilantin	296043RI	Parke Davis (Malaysia)	SIN-C1
Spain	Epanutin	H-31	Parke Davis	SP-C1
	Epanutin	I-2	Parke Davis	SP-C2
Sweden	Epanutin	3V117	Parke Davis	S-C1
	Epanutin	3V118	Parke Davis	S-C2
	Epanutin	3M921	Parke Davis	S-C3
Switzerland	Epanutin	0040073	Parke Davis (Goedecke AG, Berlin)	CH-C1
	Epanutin	0037023	Parke Davis (Goedecke AG, Berlin)	CH-C2
Turkey	Epanutin	310242	Parke Davis (Eczacibasi)	TR-C1
United Kingdom	Product A	3W793	—	GB-C1
	Product A	3W465	—	GB-C2

Assay

- *Capsules*: In the assay of capsules all countries except one reported all results between 96% and 103% of amount labeled. One brand from Argentina gave a value of 91% (AG-C1) that is lower than the limit requirement in the BP and USP (92.5 to 107.5% and 93 to 107% respectively). Ph.Eur. does not have monograph for capsules.
- *Tablets*: In the assay of tablets all the countries reported results between 94% and 103% of amount labeled. The batch in Argentina (AG-T1) and one batch in the Netherlands (NL-T2, tested in two different labs) gave a value lower than the limit requirement in the BP (95–105%). Ph.Eur. and USP do not have a monograph for tablets.

Dissolution Test

The profiles of all samples are shown in Figs. 1 and 2.

- *Capsules*: When we consider the results obtained for capsules there are clearly significant differences between the countries, and some batches within particular countries are not in compliance with the USP specification (at 30 min > 85%). Three batches in Argentina (AG-C1, 2, 3), two batches in Canada (CDN-C1, 2), two batches in Germany (D-C1, 2), two batches in Luxembourg (L-C1, 2), two batches in Mexico (MEX-C1, 2), one batch in New Zealand (NZ-C1), one batch in Singapore (SIN-C1), and two batches in Spain (SP-C1, 2) are not in compliance with the specification.
- *Tablets*: Large differences also exist among tablets throughout the world. It is likely that the tablets at the extremes of the dissolution rate are not bioequivalents but this should be confirmed by a bioavailability study. It seems clear that the three batches from Uruguay (UR-T1, 2, 3) are very slow-release tablets, as are one batch from each of

Table 4

Products Tested in Tablets

Country	Product Name	Batch No.	Manufacturer	Study Code
Argentine	Saceril	69085	Sandoz Argentina Saic.	AG-T1
China	—	930304	Yancheng Drug Manufacturer in Jiangsu Province	CHI-T1
	—	930401	Zhehe Drug Manufacturer in Hebei	CHI-T2
	—	920202	Quioguang Drug Manufacturer in Guangzhou	CHI-T3
	—	9303272	No. 2 Drug Manufacturer in Yangzhou	CHI-T4
	—	930510	No. 3 Drug Manufacturer in Beijing	CHI-T5
	—	921201	Bohai Drug Manufacturer in Tangshan	CHI-T6
Finland	Barbihydan	QKA 96 C	Laakefarmos	SF-T1
Italy	Dintoina	M009	Recordati	I-T1
	Dintoina	M010	Recordati	I-T2
Luxembourg	Diphantoine	93D02A	Wolfs	L-T1
	Diphantoine	93G07A	Wolfs	L-T2
Mexico	Fenidantoin S	402316	Byk-Gulden S.A. de C.V.	MEX-T1
	Fenidantoin S	402333	Byk-Gulden S.A. de C.V.	MEX-T2
	Fenitron	1451091	Psicofarma S.A. de C.V.	MEX-T3
	Fenitron	2470793	Psicofarma S.A. de C.V.	MEX-T4
	Nuctane	G 307254	Armstrong Laboratorios de Mexico S.A. de C.V.	MEX-T5
	Nuctane	H 206281	Armstrong Laboratorios de Mexico S.A. de C.V.	MEX-T6
Portugal	Antisacer	002K2	Laboratório Wander	P-T1
	Hidantina	94002	Laboratórios Vitória	P-T2
	OM-Hidantoine	116013	OM Portuguesa	P-T3
The Netherlands	Phenytinum natricum	930809/2 24092	Pharbita BV	NL-T1
	Phenytinum natricum	93J12/V0 0447	Pharbita BV	NL-T2
Turkey	Epdantoin	019405	Embil	TR-T1
United Kingdom	Product B	30703/1	—	GB-T1
Uruguay	Antepil	30	Laboratorio Farmaco Uruguayo S.A.	UR-T1
	Comitoina Simple	3/7050	Laboratorios Galien S.A.	UR-T2
	Hidantal Simple	9523	Servicio de Produccion Farmaceutica	UR-T3

Argentina (AG-T1) and Finland (SF-T1), and two batches each from China (CHI-T5, 6), Luxembourg (L-T1, 2), and Portugal (P-T1, 3).

Statistical Analysis

Capsules

Using cluster analysis, three products groups were found:

Group 1: AG-C1, C3; CDN-C1, C2; MEX-C1; NZ-C1; SIN-C1; SP-C1
Group 2: D-C1; L-C1; MEX-C2
Group 3: AG-C2; CH-C1, C2; CYP-C1; D-C2; GB-C1, C2; L-C2; S-C1, C2, C3; SP-C2; TR-C1

The mean solution behavior of each group is shown in Fig. 3.

There are three apparently distinct patterns of dissolution behavior which seem to be statistically different.

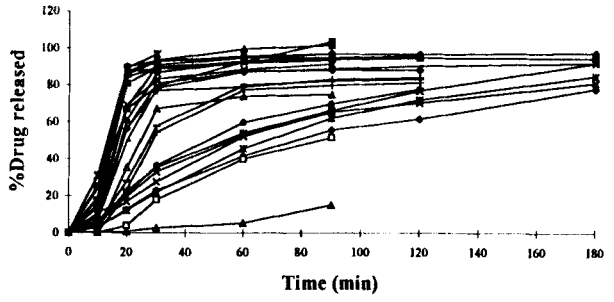

Figure 1. Dissolution profiles: capsules.

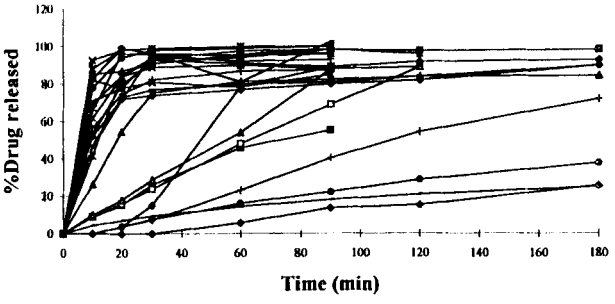

Figure 2. Dissolution profiles: tablets.

Performing the T^2 Hotelling test we can find that all two-by-two group combinations differ significantly (G1 vs. G2: $p < 0.003$; G1 vs. G3: $p < 0.000$; G2 vs. G3: $p < 0.001$).

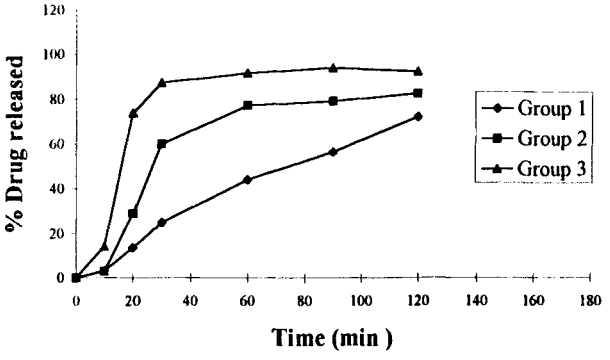

Figure 3. Solution behavior: capsules.

The t test for each time of dissolution shows that differences between group 1 and 2 are significant only for the 20th, 30th, and 60th minutes. The differences found between the first and third group, and the second and third group are significant for all measured times of dissolution.

Tablets

Cluster analysis indicated that there were two major groups with different behaviors:

Group 1: CHI-T1, T2, T3, T4, T5, T6; GB-T1; I-T1, T2; MEX-T1, T2, T3, T4, T5, T6; NL-T1, T2; P-T2, T3; TR-T1

Group 2: AG-T1; L-T1, T2; P-T1; SF-T1; UR-T1, T2, T3

In Fig. 4, one can see that group 1 shows much faster release than group 2.

Performing the means multivariate test, the differences between profiles are highly statistically significant ($p < 0.000$). Results from the univariate test show the same conclusion of significant differences of the means for all dissolution times (p's < 0.000).

Quality of Phenytoin Sodium Innovators—Comparison

We received 15 innovator products as capsules and only 4 innovator products as tablets. Details of the products tested are summarized in Tables 5 and 6.

Uniformity of Weight

Compliance with the test for uniformity of weight was found for all batches of capsules and tablets.

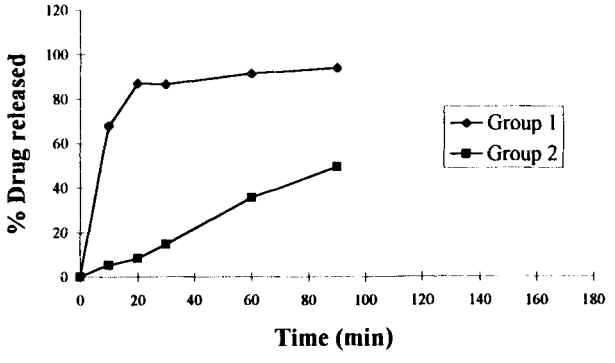

Figure 4. Solution behavior: tablets.

Table 5

Innovators Tested in Capsules in LEF

Country	Product Name	Batch No.	Manufacturer	Study Code
Argentina	Epamin	7857063	Parke Davis	AG-IC
Austria	Epanutin	0035073	Parke Davis (GmbH, Berlin)	A-IC
Canada	Dilantin	41117	Parke Davis (Canada)	CDN-IC
Cyprus	Epanutin	3N675	Parke Davis	CYP-IC
Germany	Epanutin	0035073	Parke Davis (GmbH, Berlin)	D-IC
Greece	Epanutin	3V368	Parke Davis	GR-IC
Luxembourg	Epanutin	93B01	Parke Davis	L-IC
Mexico	Epamin	801747	Parke Davis (Cia Medicinal)	MEX-IC
Singapore	Dilantin	296043RI	Parke Davis (Malaysia)	SIN-IC
Spain	Epanutin	I-2	Parke Davis	SP-IC
Sweden	Epanutin	3V117	Parke Davis	S-IC
Switzerland	Epanutin	0040073	Parke Davis (Goedecke AG, Berlin)	CH-IC
United Kingdom	Epanutin	3W793	Parke Davis	GB-IC

Disintegration

- *Capsules*: The disintegration time for all capsules was about or less than 15 min.
- *Tablets*: In regard to tablet disintegration time, only a batch from Luxembourg disintegrated after the 15 min required, whereas the tablets from the Netherlands and Italy were in compliance with the requirement. The tablets from Uruguay disintegrated at 20 min, but this is a sugar-coated tablet and has an allowed disintegration time of 60 min.

Assay

- *Capsules*: For assay of all capsules, the results obtained were between 95% and 101% of the amount labeled. Therefore they were all in compliance with the requirements of the USP.
- *Tablets*: For assay of the 4 tablets, 3 were between 97% and 100%, and 1 from Uruguay (108%) was greater than the limit required in BP.

Dissolution Test

The profiles of all innovators are shown in Figs. 5 and 6.

- *Capsules*: Despite the fact that all the capsules received have three different brand names

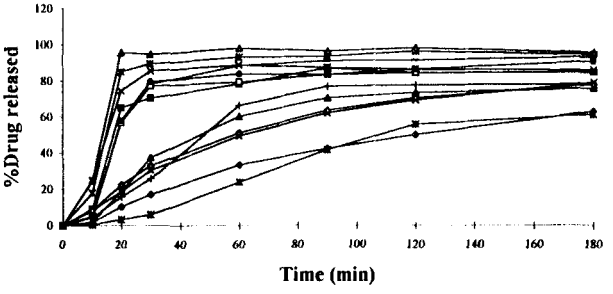

Figure 5. Innovator dissolution: capsules.

Table 6

Innovators Tested in Tablets in LEF

Country	Product Name	Batch No.	Manufacturer	Study Code
Italy	Dintoina	M009	Recordati	I-IT
Luxembourg	Diphantoine	93G07A	Wolfs	L-IT
The Netherlands	Phenytinum natricum	930809/2 24092	Pharbita BV	NL-IT
Uruguay	Comitoina Simple	3/7050	Laboratorios Galien S.A.	UR-IT

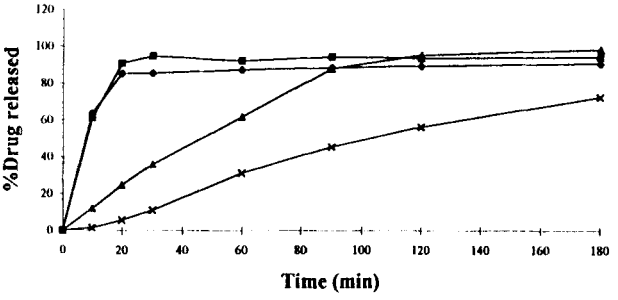

Figure 6. Innovator dissolution: tablets.

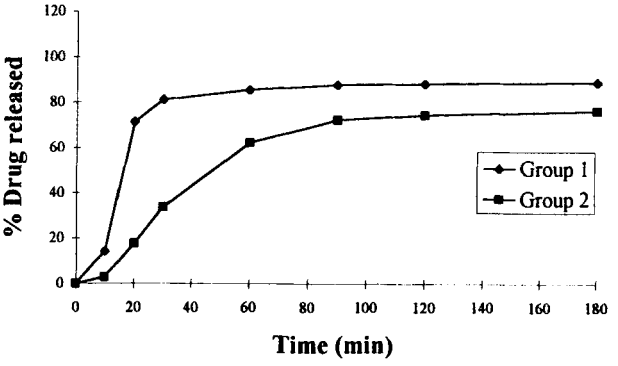

Figure 7. Cluster analysis, by country: Epanutin capsules.

(Epanutin, Dilantin, Epamin), they are all manufactured by Parke Davis. These three products can be seen to span a wide range of dissolution profile behavior with no clear distinction between the behaviors of the formulations. The percentage dissolved at each time point can be quite different for the innovator products. Considering the requirement of USP (at 30 min > 85%), just 3 capsule innovator products were in compliance with the USP: capsules from Cyprus, Switzerland, and Sweden.

- *Tablets*: The four innovator products as tablets are from different manufacturers. The tablets from the Netherlands and Italy are in compliance with the requirement of percentage dissolved greater than 85% at 30 min, whereas the tablet from Luxembourg achieved this value only at 90 min. It was observed that the tablet from Uruguay is a particularly slow release product (73% at 180 min).

Statistical Analysis

Capsules

Since 11 countries used Epanutin as the reference product for bioequivalence studies, it would be interesting to evaluate whether the same product would yield the same results in the different countries which produce it. Performing cluster analysis, we found two groups which seem to behave in a different way (Fig. 7).

Group 1: Austria, Cyprus, Germany, Spain, Sweden, Switzerland, United Kingdom
Group 2: Greece, Luxembourg

By the Hotelling test, one can see that the differences between the means of drug release values for each group are statistically significant ($p < 0.001$) for all dissolution times. At each time point all differences of the means are statistically significant by the t test except for the 10-min result ($p = 0.050$).

Since the analysis shows that the same reference product behaves in different ways, depending on the country which produces it, we should ignore the commercial name and try to characterize those which behave in similar way. Including all of the results obtained by LEF for the 13 country innovators, we again obtained two apparently different groups of results (Fig. 8):

Group 1: Argentina, Canada, Greece, Luxembourg, Singapore
Group 2: Austria, Cyprus, Germany, Mexico, Spain, Sweden, Switzerland, United Kingdom

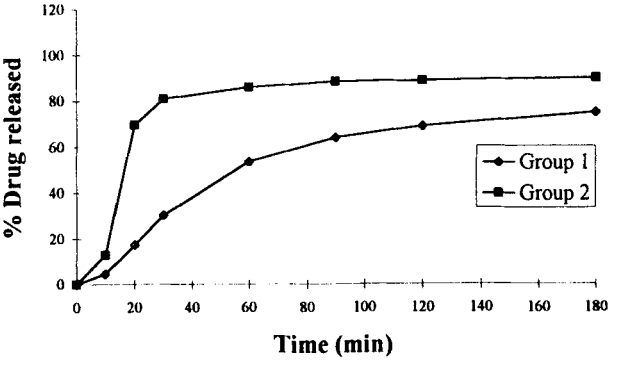

Figure 8. Cluster analysis, by behavior: Epanutin capsules.

By multivariate analysis the mean results are statistically different ($p < 0.001$), and for each dissolution time the differences remain significant.

Tablets

Only 4 countries presented tablet innovators. Even with such low representation, one can detect two distinct release behaviors as shown by Fig. 9. Group 1 comprises Italy and The Netherlands; Group 2, Luxembourg and Uruguay.

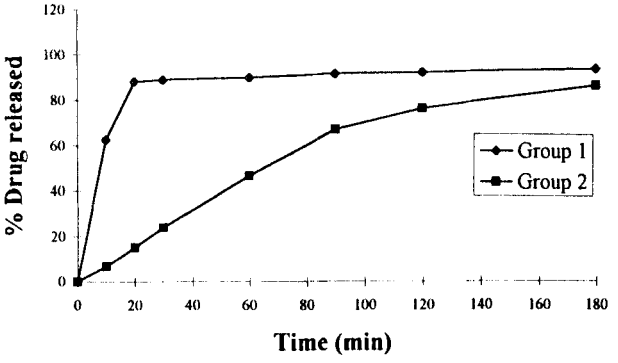

Figure 9. Release behavior: innovator tablets.

Because there are only two observations in each group, it is not possible to perform the multivariate test for differences of the means. Comparing the group means for each dissolution time we did not find significant differences ($p > 0.100$). This result is mainly explained by the low representation within each group.

Assessment of Interlaboratory Variation

Dissolution Test Calibration

All participants submitted the data for the USP Official Reference Standard Prednisone Tablets (dissolution calibrator, disintegrating), batch J, using apparatus 1 (basket) at 50 rpm. Figure 10 shows the different results. The results from Argentina, China, and Cyprus were higher than the limits suggested by the USP (6–23% at 30 min). All the other countries had results between 8% and 21%.

Standard Sample Results

To assess the interlaboratory variability, 22 laboratories of 19 countries returned results for a standard sample.

Assay

Concerning the total phenytoin content, all the results were between 94% and 101% of the nominal content.

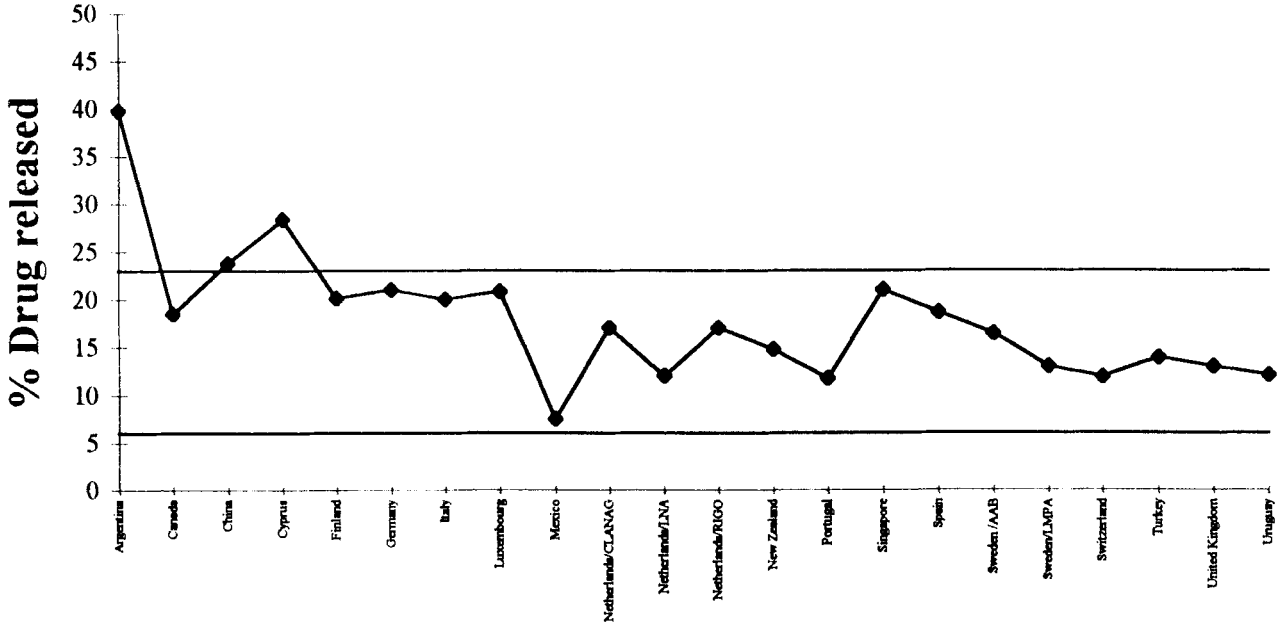

Figure 10. Dissolution test calibration results by country.

Mexico reported a slightly high result (108%) in the assay.

Dissolution Test

Considering the results of the dissolution test carried out by all the laboratories we found that:

- At 10 min there were large differences between the results of the countries (range from -29.4% to +57.2% of the mean), corresponding to a percentage dissolved between 22% and 49%.
- At 20 min the differences between the results obtained were less than at 10 min (range from -16.8% to +19.8% of the mean).
- At the other points of testing, the results were closer and all lay within a range of variation of ±10%.

Figure 11 shows the dissolution profiles for the standard sample analyzed in all participating laboratories.

After analyzing the results supplied by all the participating laboratories that used the dissolution calibrators and the results of the standard sample, we consider that we may compare the results from the different laboratories as a whole. By cluster analysis and using the same criteria as before to enhance different groups (based on Euclidean distances), we identify only one group which contains all the 22 laboratory results and we conclude that there is no significant variability between laboratories.

But if we want to be requirable, we reduce the acceptance level of Euclidean distances (e.g., to 50) and we can distinguish two different groups (Fig. 12):

Group 1: Argentina, Cyprus, Germany, Italy, Mexico, Netherlands/LNA, New Zealand, Portugal, Singapore, Spain, Sweden/AAB, Sweden/LMPA, Turkey, United Kingdom, Uruguay

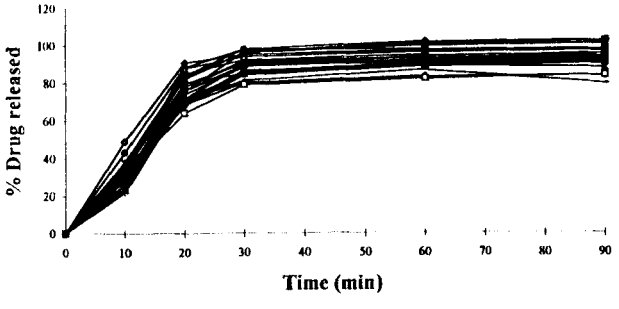

Figure 11. Dissolution profiles for standard sample: all laboratories.

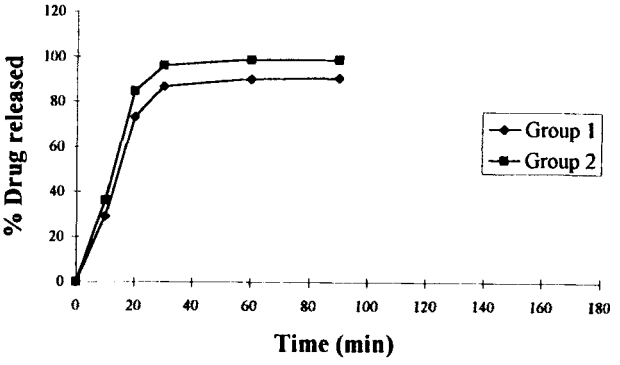

Figure 12. Dissolution profiles for standard sample: reduced Euclidean distance acceptance level.

Group 2: Canada, China, Finland, Luxembourg, Netherlands/CLANAG, Netherlands/RIGO, Switzerland

The second group shows slightly higher release values.

By multivariate analysis the differences of the means between groups are highly significant ($p < 0.001$). For each time point, the statistical significance of differences between means maintains $p < 0.05$.

Dissolution profiles of the market products, innovators, and standard product from individual participating countries are shown in Fig. 13.

CONCLUSIONS

It seems clear that the different brand names of capsules, containing 100 mg of phenytoin, from the respective countries present in vitro dissolution characteristics that appear to demonstrate the existence of 3 types of products releasing drug at different rates (Fig. 3). In the case of the comparison of tablet products we identified two major groups of products having distinct release behavior (Fig. 4).

Results for the innovator products, obtained by LEF, indicate that the Epanutin capsules produced in the respective countries do not have identical dissolution characteristics and can be classified into two significantly different groups (Fig. 7). All innovator products including Epanutin could similarly be classified into a faster- and slower-dissolving group (Fig. 8). Within the innovator tablets we found enormous differences among the four brands. Large differences were observed between innovator tablets from 4 different countries carrying 4

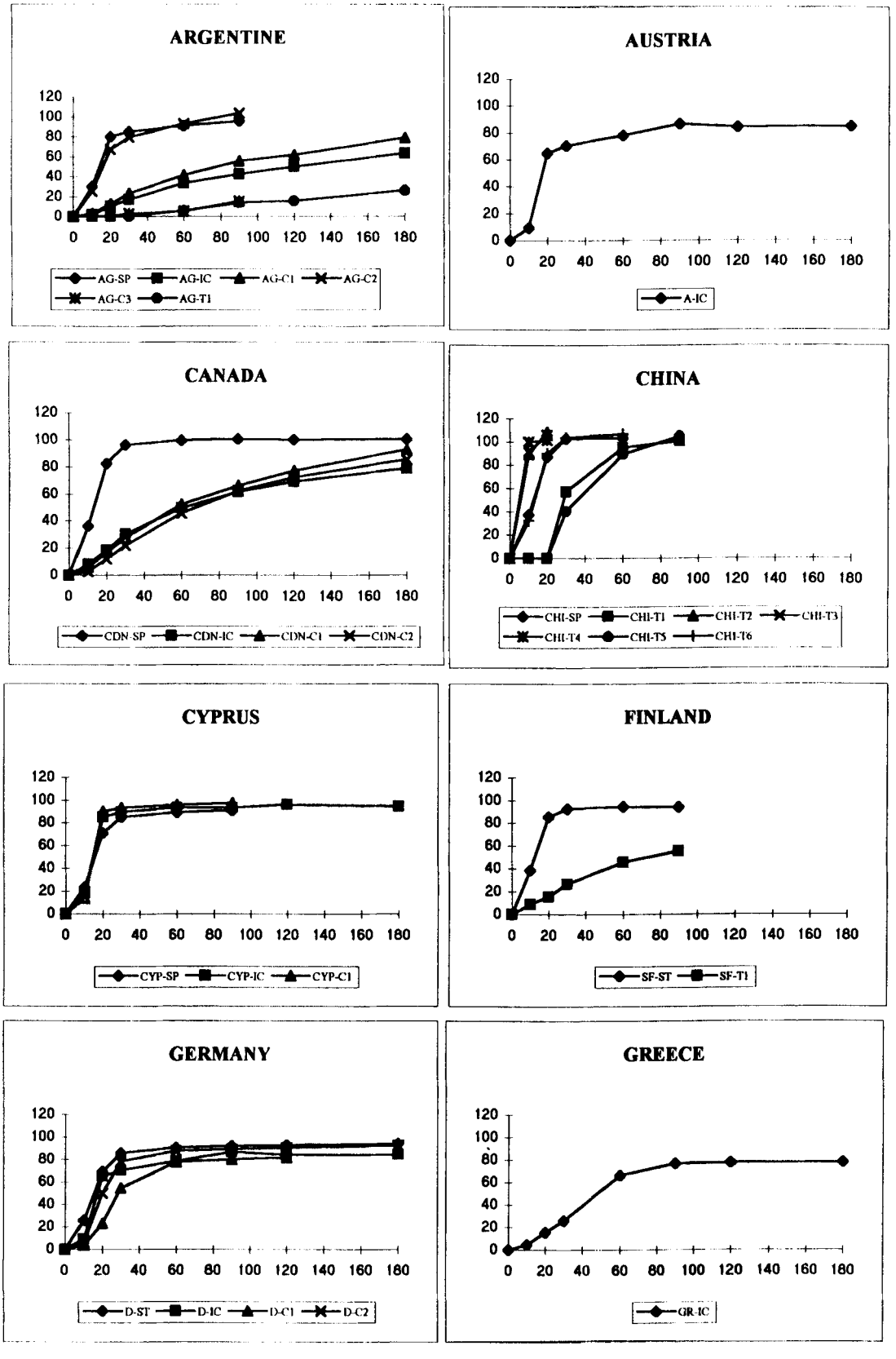

Figure 13. Percent drug released vs. time (min): market products, innovator formulations, and standard product, by country.

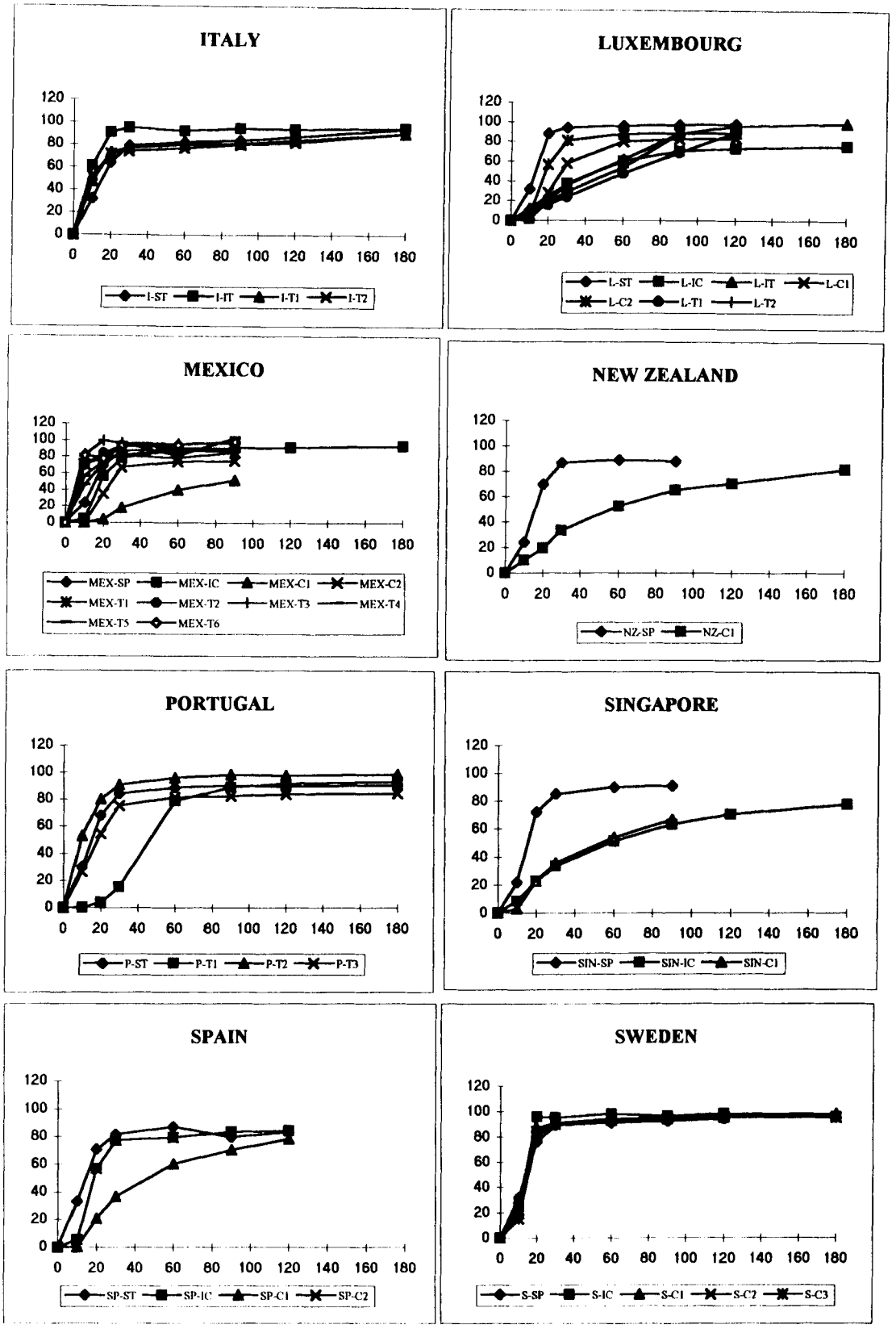

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Figure 13. Continued.

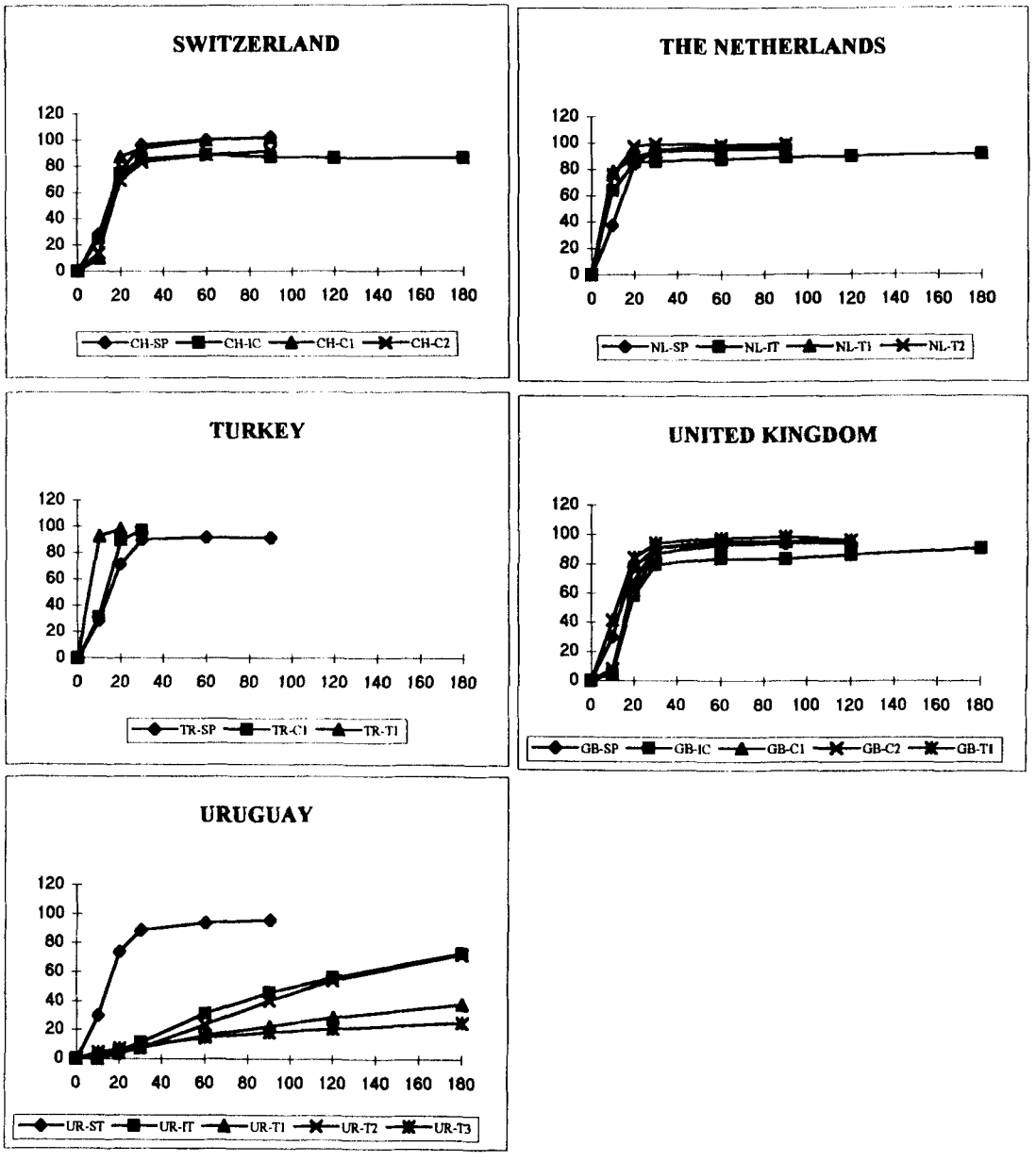

Figure 13. Continued.

different brand names. Two products displayed rapid dissolution profiles and two were substantially slower (Figs. 6 and 9).

Some variability was observed in the interlaboratory comparison of dissolution results using the USP standard prednisone tablets (Fig. 10) and standard samples supplied by LEF (Fig. 12). In order to obtain more reliable results in the assessment of interlaboratory variability, we suggest that a study protocol should specify at least 12 individual dissolution results for previously defined dissolution times of the standard sample.

The degree of variability reported here for sodium phenytoin capsule and tablet products raises definite questions concerning the bioequivalence of the different products available worldwide and between innovator products of the same brand name manufactured at different sites. Although some results may be influenced by testing procedures carried out in particular laboratories,

this does not appear to contribute a significant source of variability in the presented results.

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