DRUG DEVELOPMENT AND INDUSTRIAL PHARMACY, 21(8), 925-942 (1995)

EVALUATION OF PHARMACEUTICAL QUALITY OF PREDNISONE TABLETS FROM MULTINATIONAL MARKETS*

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ABSTRACT

This report describes results of a collaborative study in which samples of the 5 mg strength of prednisone tablets were evaluated following a common protocol based on European (Ph. Eur.) and US Pharmacopeial (USP) specifications. Several tests including, identification, content uniformity and dissolution were performed. Laboratories from 16 countries submitted data representing 42 products obtained from the respective local markets. There were no reported abnormalities in general appearance and identification of the products evaluated. Most products met the requirements for assay and content uniformity. Dissolution results showed that 11 lots did not meet the USP S1 stage *Tolerance Criterion*, whereas products from Greece (one lot) and Sweden (two lots) would not meet the dissolution requirement of USP even at the S3 stage, i.e. these lots would be rejected. Overall variability (% CV) in percent drug release values at different sampling times for the tested products and those of USP calibrator tablets were not significantly different from each other. To assess the potential effect of dissolution characteristics on *in vivo* bioavailability, the percent drug release values were also evaluated using a logarithmic-probability

*In collaboration with the study group (Table 2) of the OLMCS of the FIP

regression approach as described in the literature. The results suggest that, except for the products which would not meet USP criterion (S3 Stage), other tested products would not be expected to have bioavailability problems.

INTRODUCTION

The synthetic glucocorticoid, prednisone, and its reduced form prednisolone are prescribed for the treatment of a wide variety of diseases for their anti-inflammatory and immunosuppressant activities (1). The pharmacological activity of prednisone is due to its biotransformation to prednisolone which usually occurs in liver (2).

To establish the quality of a pharmaceutical product, at production or marketing stages, it is evaluated using a variety of physicochemical methods generally described in different compendia, such as British (BP) and the United States (USP). Deutsches Arzneiprüfungsinstitut, Munich, Germany, previously reported three comparative drug quality studies of prednisone tablets from the German market (3-5). Results of these studies (3,4) showed that there were deficiencies in quality of the marketed products; in particular, marked differences in *in vitro* dissolution profiles were reported among different batches and between tablets of the same batch (5).

Generally, the drug product quality tests are performed within individual countries using methods listed in one of compendia e.g. USP, BP, or Ph. Eur. Therefore, similar products, even from the same multinational pharmaceutical company may be evaluated according to different criteria. Therefore, it is possible that variables such as different manufacturing sites, sources of raw material, or processes could create subtle formulation differences which could result in changes in physico-chemical properties including *in vitro* drug release characteristics and could impact on *in vivo* performance.

The aim of the study was to assess the quality of prednisone products following a common protocol for a more appropriate comparison among products from different markets.

MATERIAL AND METHODS

The study protocol was drafted jointly by the Deutsches Arzneiprüfungsinstitut and Zentrallaboratorium Deutscher Apotheker, ZL, and was finalized following discussions at the meetings of the Section of Official Laboratories and Medicines Control Services (OLMCS) of International Pharmaceutical Federation (FIP), Eschborn, Germany, June 1991, and FIP Pharmacy World Congress, Washington, DC, USA, September 1991. The proposed methods were based on the requirements of the European (Ph. Eur.) and the United States Pharmacopeia (USP). An abbreviated version of the study protocol is described in Table 1.

It was proposed that if possible, each laboratory submits results by analyzing two lots of 5 mg strength of prednisone tablets marketed in the participating country. Further, it was recommended that one sample should be obtained from the market i.e, retail pharmacy or wholesaler and the second sample would be procured directly from the manufacturer.

It was required that the dissolution apparatus should have been calibrated following the Suitability Test as described under the general chapter on dissolution in the USP XXII.

Data presentation and analysis: Distributions of individual, mean and co-efficient of variation values are presented as boxplots (Figure 1) in which each of the four quartiles represents one-quarter of the values. Values which are outside the quartiles are considered as potential outliers(SPSS software, SPSS Inc., IL).

For logarithmic-probability plots, percent drug-released values were converted to *z* scores using an inverse probability function by the application of computer software SAS (SAS Institute, NC). To avoid null values, in cases where percent drug release values were 100 or greater values were substituted with 99.9.

RESULTS AND DISCUSSION

The data were submitted by laboratories from 16 countries. Table 2 describes the names of participating institutions and the investigators. All

TABLE 1
Protocol Requirements for the Collaborative Study.

TEST*	DESCRIPTION
Identification (USP)	IR Spectrum and colour test
Content Uniformity (USP)	Content of active ingredient of 10 tablets
Assay (USP)	Using HPLC method
Disintegration (Ph. Eur.)	Run for 15 minutes for a set of six tablets
Dissolution (USP)	USP Apparatus 2 (Paddle Method) Medium: Water (500 mL for < 10 mg tablets or 900 mL for ≥ 10 mg tablets Agitation: 50 rpm Detection: UV (242 nm) Sample: 6 Tablets Sampling times (5.0 ml at 5, 10, 15, 30 and 60 minutes, solvent replacement by test medium

* Enclosures refer to the pharmacopeial reference.

participants provided results with 5 mg strength tablets, mostly describing multiple products and lots. Details of the products tested are summarized in Table 3.

There was no reported abnormality in the physical test requirements of the products analyzed. Therefore, all preparations investigated in this study fulfilled the requirements of USP XXII for identification tests.

The results concerning assay and content uniformity are presented in Table 4. In this table minimum and maximum values are given for the products of the different countries, representing results reported for all products tested from the local market. The US and European pharmacopeia

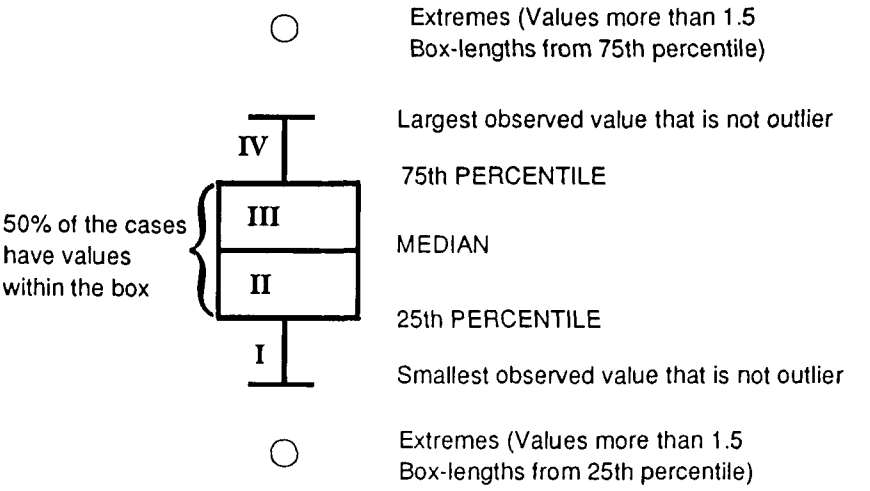

FIGURE 1

Annotated sketch of a boxplot.

have different requirements for deviation in the assay values, which are ±10 and 5%, respectively. All products met the USP requirement, however, products from two European countries (Finland and Portugal) would not meet the EC requirements of 95 to 105% (6). Results of content analysis were not submitted by the laboratories from Canada and Greece where as French laboratory did not submit content uniformity results.

Except for products from Greece, which showed higher content uniformity values (89-130%), all products were within the required acceptance limits of 85 to 115% for tablet formulations. Content uniformity values were between 89 - 125% for one Greek formulation and between 89 - 130% for the other formulation, thereby failing to conform with the requirements.

***In vitro* Dissolution**: Eighteen sets of data describing the drug release profiles of USP calibrator tablets were submitted. Prednisone USP calibrator of lots H, I and J were analyzed by different laboratories (Figure 2). The specification of percent prednisone dissolved at 30 minutes using

TABLE 2

Names of the Institutions and Investigators Participated in the Study.

COUNTRY	INSTITUTION	INVESTIGATORS
1. Argentina	Faculty of Pharmacy and Biochemistry, University of Buenos Aires	M. Pizzorno
2. Canada	Bureau of Drug Research, HPB, Health Canada, Ottawa.	I.J. McGilveray, S.A. Qureshi
3. Chile	Departamento de Farmacia, P. Universidad Católica de Chile, Santiago	Prof. R.P. Reves
4. Denmark	Medicines Division, National Board of Health, BrØshØr, Denmark	M. Handlos
5. Finland	Lääkelaboratorio, National Medicines Control Laboratory, Helsinki	A. Kaukinen
6. France	Faculty of Pharmacy, University of Clermont-Ferrand, France	J.-M. Aiache
7. Germany	Zentrallaboratorium Deutscher, Apotheker and Deutsches Arzneiprüfungsinstitut, Eschborn	H. Blume, S. L. Ali, M. Siewert, and M. Steinigen
8. Greece	Department of Pharmacy, Aristotelion University of Thessaloniki, Thessaloniki	M. Georgarakis
9. Luxemburg	Laboratoire National de Santé, Division Chimique Toxicologique et Pharmaceutique	J.-L. Robert
10. Netherlands	Laboratorium der Nederlandse Apothekers, S-Gravenhage	F. J. Van de Vaart
11. Paraguay	Faculty of Pharmacy and Biochemistry, University of Buenos Aires	G. Steemann A. Segall
12. Portugal	Faculty de Farmácia, Laboratório de Biofarmácia, Lisboa	A. Farinha
13. Spain	Ministerio de Sanidad Y Consumo, Centro Nacional de Farmacobiologica, Madrid	A. Valasquez
14. Sweden	Läkemedelsverket, Medical Products Agency Division of Pharmacy, Uppsala	J.-O. Waltersson M. Haraldsdóttir
15. Switzerland	Interkantonale Kontrollstelle für Heilmittel, Bern	U. Salzmann S. Steiner
16. United Kingdom	British Pharmacopeia Commission, Medicines Testing Laboratory, Edinburgh	A. G. Davidson

apparatus 2 at 50 rpm was met by all participants who submitted the data for the calibrators.

Sixteen participating countries submitted 62 sets of data representing 58 lots of 42 prednisone products. All products tested were of 5 mg strength. Some laboratories presented only mean values for six tablets with percent coefficient of variation values without data for individual tablets. Figure 3 shows the distribution, in boxplot format, of the percent drug-released values for individual tablets.

Figure 4 describes the distribution of individual values excluding those which would not meet the USP S3 criterion i.e. percent drug release value for at least one of the tablets is less than 55% (Q-25) dissolved in 30 minutes. Products from Greece (lot # 3.111) and products from Sweden (lot RF 9914 and RH 1043) would be rejected and were excluded from the further analyses.

Figure 4 also includes distribution of the percent prednisone released from various lots of the USP calibrators. The USP XXII monograph for prednisone tablets requires that at the S1 stage criterion, the dissolution should not be less than 80% (Q) of the labelled amount of prednisone in 30 minutes. In addition to the products from Greece and Sweden as described above, products from Chile (lots 2ABBA1 & 2ABBA), France (lot 245), Germany (lot 0885E0) Paraguay (lots 1919121 & 3069062) and from Spain (lot E-2 & G-2) did not meet the S1 stage criterion.

Figure 5 shows the spread of mean percent drug released (A) and CV values (B) for both tested product lots and USP calibrators. It is apparent that the distribution of CV values for the tested product is similar to that of the calibrators. As a representation of drug release characteristics of the tested products, mean percent drug release profiles from individual participating countries are given in Figure 6.

***In vitro/in vivo* Correlation Considerations:** The rate and extent of *in vitro* drug release are often important determinations of the *in vivo* drug-release and absorption from a formulation. Their determination is a

TABLE 3

Details of the Tablet Preparations Analyzed

COUNTRY	PRODUCT NAME	Batch No.	Manufacturer
Argentina	1. Meticorén	2/04/01 2/05/01	Schering-Plough
Canada	1. APO PREDNISONE	T4360	APOTEX
	2. APO PREDNISONE	T4362	APOTEX
	3. PREDNISONE	390691	Drug Trading Co.
	4. PREDNISONE	BA30	KENRAL INC.
	5. NOVOPREDNISONE	1901240	NOVOPHARM
	6. NOVOPREDNISONE	1638680	NOVOPHARM
	7. PREDNISONE	207	PRO DOC LABS.
	8. PREDNISONE	306	PRO DOC LABS
	9. DELTASONE	A500	UPJOHN
Chile	1. A	1, 2	
	2. B	1, 2	
Denmark	1. Prednison "DAK" tabletter (31.10.97)	L 411990	Nycomed DAK A/S
	2. Delcortin tabletter (31.07.97)	X 24 B	L Ø Vens Kemiske Fabrik, Ballerup
	3. Delcortin tabletter (30.06.97)	A 24 A	
Finland	1. Prednisone	RB 2 - 1	Orion
	2. Prednisone	RA 1 - 2	Orion
	3. ME-KORTI	REA 10 B	Lääkefarmos
France	1. Cortancyl	245	
Germany	1. Decortin 5 (31.12.93)	100 1125	Merck
	2. Decortin 5 (31.12.93)	344 1635	Merck
	3. Prednicorm	1219	Cormontapharm
	4. Prednison "Berco"	1219	Berco
	5. Prednison-Dorsch	910907	Dorsch
	6. Prednison Ferring	91185	PharmaGalen
	7. Prednison Ferring (30.06.95)	91073	PharmaGalen
	8. Prednison-ratiopharm	0885E0	ratiopharm
	(31.12.98)	0896B1	ratiopharm
	9. Prednison-ratiopharm	00003901	Börner
	10. Prednison Sanhelios	022051	Sanorania
	(20.06.96)	023071	Sanorania
	11. Predni-Tablinen (30.06.96)	175	Ciba Pharma
	12. Predni-Tablinen	177	Ciba Pharma
	13. Ultracorten		
	14. Ultracorten		

TABLE 3 (Cont'd)

COUNTRY	PRODUCT NAME	Batch No.	Manufacturer
Greece	1. Chrocart	3.111	XP 3.111
	2. Chrocart	2-18	XP 2.17
Luxemburg	1. Prednicort	91 E 28	Continental Pharma
Netherlands	1. Prednisonum	88601/0103246	Genfarma
	2. Prednisonum	91F03KA	Pharmachemie
	3. Prednisonum	90L03A	Centrafarm
	4. Prednison	91D24A	Katwiyk farma
	5. Prednisonum	910130/200080	Pharbita
	6. mp-prednison	901026/442	Multipharma
Paraguay	1. Prednicort	1919121	Catedral
	2. Prednicort	3069062	Catedral
Portugal	1. Meticarten	1 ABBA 03	Essex
	2. Meticarten	1 ABBA 02	Pharmaceutica
Spain	1. Innovator	G4	
	2. Innovator	G5	
	3. Generic	G1	
	4. Generic	E2	
Sweden	1. Deltison	RF 9914	Ferring AB
	2. Deltison	RH 1043	Ferring AB
Switzerland	1. Prednisone	1087963	Merck
	2. Prednisone	0196843	Merck
	3. Prednisone Streuli	437796	Streuli
	4. Prednisone Streuli	460896	Streuli
	5. Prednisone Galepharm	0791	Apotheke Hotz
	6. Prednisone Galepharm	1290	Apotheke Hotz
United Kingdom	1. Prednisone A	28261	
	2. Prednisone B	28360	

first step in searching for *in vitro* dissolution/*in vivo* absorption associations. To compute the rate of dissolution, it is useful to linearize dissolution results i.e., percent-drug release *vs* time. Among other techniques, the use of a logarithmic-probability regression approach has been reported (7, 8) for such linearization to compare the drug release profiles of different brands/lots of prednisone products. Using both a paddle-stirrer dissolution technique, similar to the USP Apparatus 2 and a spin-filter procedure,

TABLE 4

Ranges (Min - Max) of the Reported Values for Assay and Content Uniformity of the Tested Products.

Country	Assay (%)	Content Uniformity (%)
Argentina	96.0 - 102.0	91.0 - 112.0
Canada	-	97.8 - 107.0
Chile	98.0 - 103.6	95.2 - 106.8
Denmark	99.8 - 102.6	96.2 - 102.4
Finland	102.0 - 106.0	96.0 - 103.0
France	102.0 -	-
Germany	95.1 - 101.9	91.8 - 104.6
Greece	-	89.0 - 130.0
Luxemburg	103.0 -	98.0 - 106.0
Netherlands	97.0 - 104.0	98.0 - 106.0
Paraguay	92.0 - 94.0	91.0 - 95.0
Portugal	104.0 - 106.0	97.0 - 103.0
Spain	99.0 - 104.0	100.0 - 105.0
Sweden	100.0 - 103.0	92.0 - 115.0
Switzerland	102.0 - 104.0	97.0 - 111.0
United Kingdom	96.0 - 97.0	94.0 - 104.0

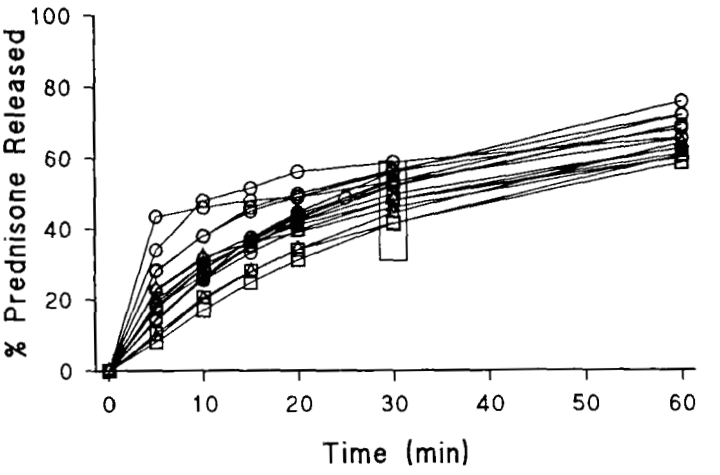

FIGURE 2

Mean drug release profiles of USP calibrators (prednisone) using Apparatus 2 at a paddle speed of 50 rpm. Lot: △=I, ○=J, □=H. The rectangle represents the boundaries of the requirements of percent prednisone released at 30 minutes from the USP calibrators.

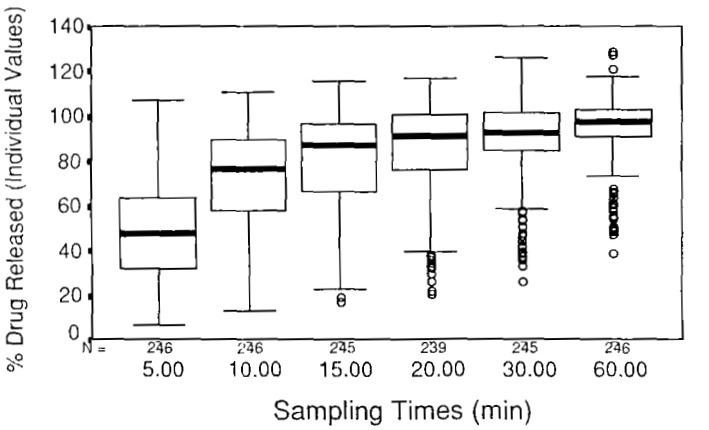

FIGURE 3

Boxplots of percent drug release values for the prednisone (5 mg) tablet products from 16 countries representing 42 products. Dissolution experiments were conducted using USP Apparatus 2 (Paddle Method) with 500 mL of dissolution medium, paddle speed set at 50 rpm. "N" denotes number of values for each time point. For the explanation of the boxplot diagram refer to Figure 1.

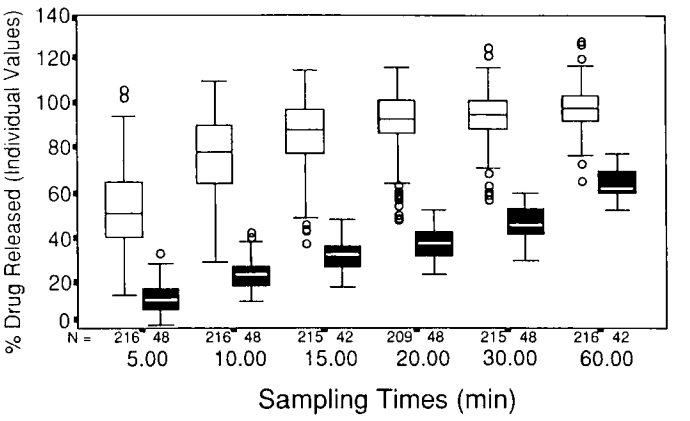

FIGURE 4

Distribution of percent drug release values for prednisone calibrators (■) and products (□), excluding lots which did not meet the USP criterion of Q-25%. Dissolution conditions: Apparatus 2, Paddle Speed=50 rpm, Medium=Water (500 mL for the products, 900 mL for the calibrator). "N" denotes the number of values for each time point. For the explanation of the boxplot symbols refer to Figure 1.

Milsap et al (9) have reported that a linear relationship exists between the *in vitro* drug release and *in vivo* time to reach half-maximal plasma prednisone concentrations in normal volunteers after a "cut-off" point. Based on the data obtained using 0.1 N HCl as dissolution medium with the paddle-stirrer apparatus at a rotation speed of 50 rpm, they reported that if 16 and 50% of the drug were released in less than 13.7 and 21.5 minutes respectively, then there were no significant differences in the time to reach half-maximal plasma prednisone concentrations of the drug products. However, if the times required for 16 or 50% dissolution of the contents are more than the "cut-off" points of 13.7 and 21.5 minutes, then the *in vivo* drug parameter is linearly correlated to the *in vitro* drug release rate. It was reported that the results obtained were in agreement with those reported earlier (8) where the same products were tested using water as dissolution medium.

Using this approach, the data obtained from different laboratories in the present study were also analyzed. For the linearization, the

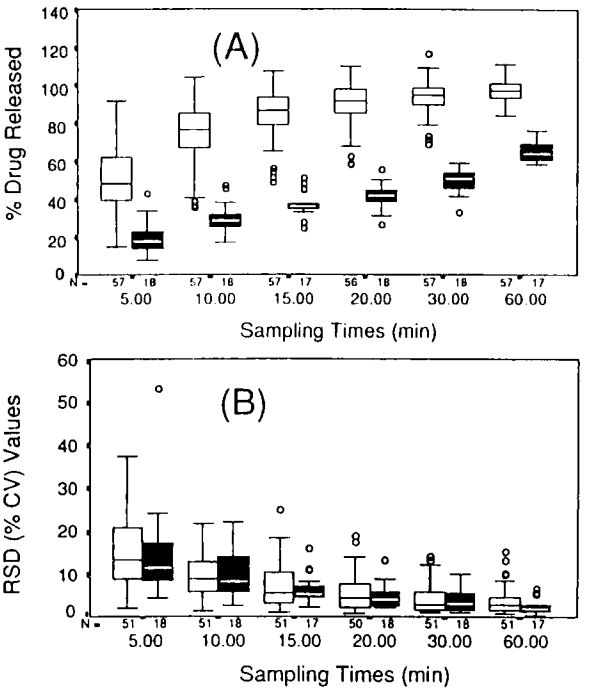

FIGURE 5

Distribution of mean percent drug release values (A) and percent CV values (B) for prednisone calibrators and products, excluding for lots which did not meet the USP criterion of Q-25%. "N" denotes the number of samples in each group at the individual sampling time points. □=Products, ■=USP Calibrator. For the explanation of boxplot symbol refer to Figure 1.

percentages of drug dissolved were converted to Z values (z score) using the inverse normal-probability function. For the individual sets of data, estimates of slope (s) and intercept (I) were obtained by fitting the linear regression model according to: $Z = I + s (\log t)$, where t represents time.

Table 5 summarizes the results of the regression analysis. Data from one set were not included in the regression analysis due to lack of

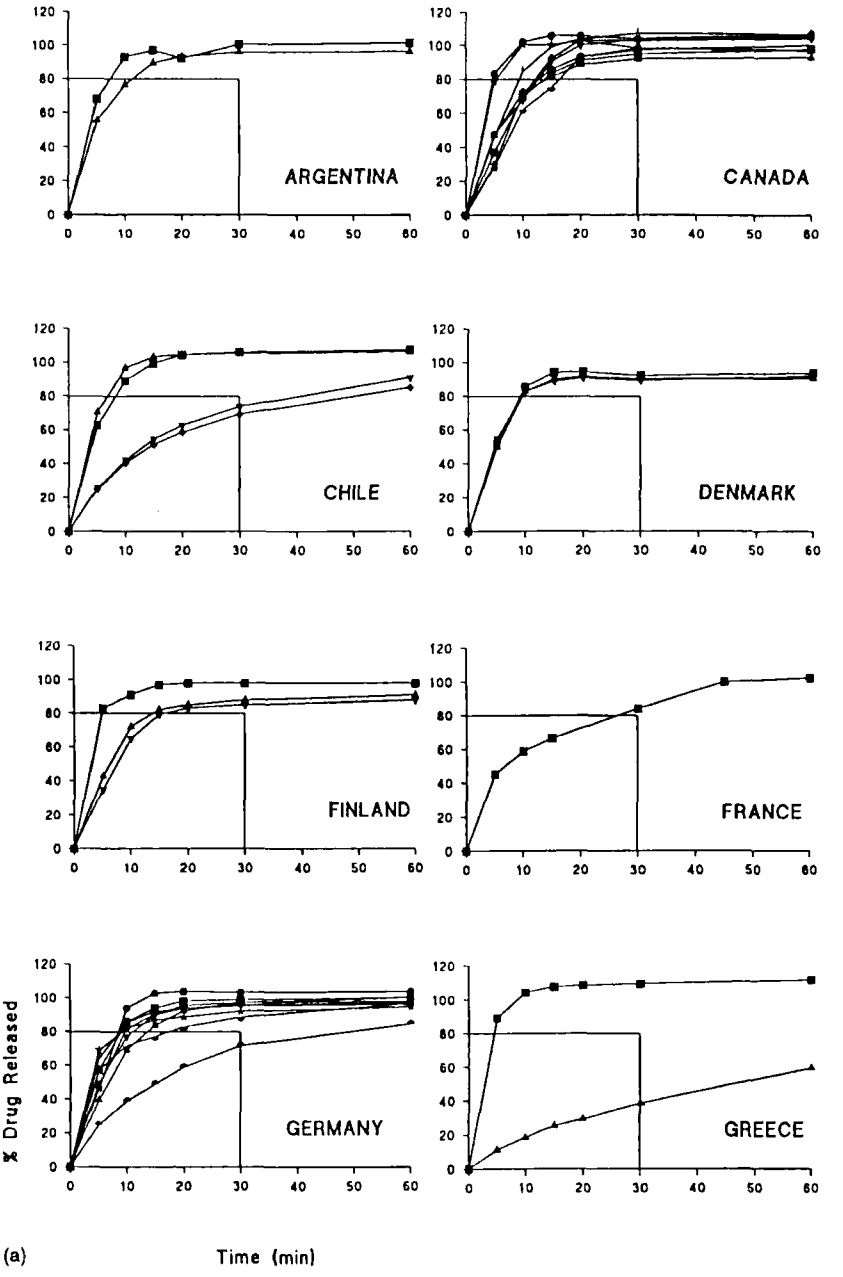

FIGURE 6

Mean drug release profiles of 5 mg prednisone tablets representing products from individual participating countries. Dissolution conditions: Apparatus 2 (Paddle Method), Dissolution medium=500 mL (Water); Paddle speed=50 rpm. Grid represents the USP *Tolerance Criterion* i.e. not less than 80% (Q) dissolved in 30 minutes.

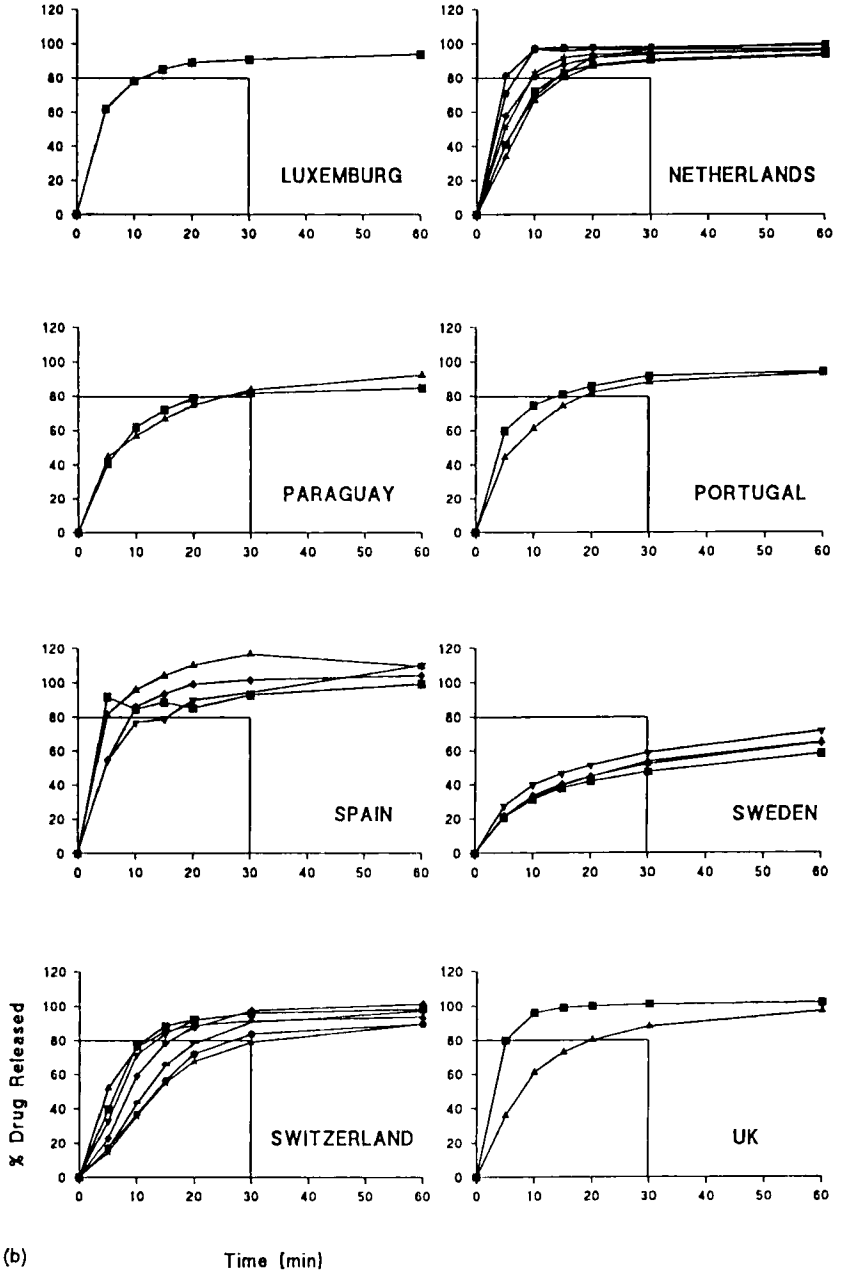

FIGURE 6. Continued

TABLE 5

Summary (n=61) of Parameters Obtained from Regression Analysis of z Scores (Z) for the Percent Drug Dissolved *vs* log(time).

	R^2	Intercept (I)	Slope (s)
Min	0.452	-3.326	0.339
Max	0.999	1.010	1.642
Mean	0.874	-1.246	0.836
SD	0.141	0.966	0.333

linearity. It is considered unlikely that this very rapidly dissolving lot would exhibit bioavailability problems.

Table 6 summarizes the estimated time required for 16 and 50% of drug-release computed using the equation $t = e^{(1-Z)/s}$.

The estimated dissolution time for 16% drug release was less than 8.5 minutes for all products. Except for four lots, the estimated dissolution time for 50% drug release was less than 21.5 minutes. Therefore, from the dissolution rate analyses based on the logarithmic-probability regression method, all but three lots are expected to have similar and acceptable *in vivo* characteristics. Products from Greece (Chocort, Lot #3.111) and Sweden (Deltison, lots # RF 9914, including the repeat, & RH 1043) with estimated dissolution times for 50% drug-release of 45.9, 34.1, 25.6 and 26.2 minutes, respectively, exceeded the "cut-off" point, and therefore, could be considered more likely to exhibit bioavailability problems.

The USP monograph on prednisone requires that not less than 80% of drug (Q) should be dissolved in 30 minutes. Considering percent drug release from individual tablets of less than 55% i.e. *Q*-25%, three lots would not meet this standard. The three lots are the same lots which failed to meet the criterion of the estimated time required for 50% dissolution based

TABLE 6

Summary Results (n=61) of the Estimated Times to Dissolve 16 and 50% of Drug from Various Lots.

	For 16% Release (min)	For 50% Release (min)
Min	0.01	0.12
Max	8.21	45.89
Mean	1.81	6.95
SD	1.59	8.22

on the method of logarithmic-probability transformation. Therefore, the USP criterion and the probability method for 50% dissolution appear to give similar results for these samples.

Using the paddle method, the estimated time required for 50% dissolution correlate better than the 16% dissolution time (r = 0.993 vs. 0.957) with the *in vivo* parameter. Based on this observation, it can be concluded that only three lots out of 42 lots tested might be expected to show undesirable *in vivo* absorption characteristics.

ACKNOWLEDGEMENT

The authors would like to thank Mr. Johannes Kraemer of Deutsches Arzneiprüfungsinstitut, Eschborn, Germany for useful suggestions.

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