DRUG DEVELOPMENT AND INDUSTRIAL PHARMACY, 21(19), 2167-2186 (1995)

A MULTINATIONAL SURVEY OF THE QUALITY OF CARBAMAZEPINE TABLETS

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ABSTRACT

The results of a multinational survey of the quality of carbamazepine tablets are reported. A total of 22 laboratories in nineteen countries worldwide participated in the study conducted under the auspices of the Official Laboratories and Medicines Control Services (OLMCS) Section of FIP. The results of tests conducted on 86 samples representing at least 34 different products, comprising the innovator's product Tegretol, 13 other branded products and 20 generic products, are presented. Most products fulfilled the requirements of pharmacopoeial quality standards. However, there were marked differences in dissolution behaviour which suggest that not all products are bioequivalent with each other. Most of the products tested would not comply with a requirement for the percentage of carbamazepine released at 15 minutes, that is proposed for inclusion in the USP monograph for Carbamazepine Tablets.

INTRODUCTION

The maintenance of blood levels of carbamazepine, like that of other anticonvulsant drugs, within a narrow therapeutic range is necessary to avoid loss of seizure control and to reduce potential side effects [1]. Tegretol, which was introduced in the 1960s, is manufactured with sieved active substance of relatively large particle size. Consequently, the *in vivo* and *in vitro* release profiles of Tegretol Tablets are relatively slow. The use of drug substance of different particle size may lead to slower or quicker dissolution rates than that of Tegretol, resulting in different t_{max} and/or C_{max} values and possible fluctuations outside of the narrow therapeutic window for carbamazepine. Marketing authorisation of one carbamazepine product was withdrawn in Norway in 1991 owing to significant differences in dissolution rates from that of Tegretol [2]: another product was recalled in 1992 in the UK because it was not manufactured in accordance with its product licence.

Carbamazepine is slowly but fairly completely absorbed from the GI-tract. Its rate of absorption is variable and its biovailability can differ markedly among different formulations. A recent study in the United States of America showed that there were significant differences in rate and extent of absorption among three generic carbamazepine products and Tegretol [3]. The same study showed that an *in vitro* test, based on the experimental conditions of the USP dissolution test for Carbamazepine Tablets, gave a good relationship between the percentage dissolved and the C_{max} and AUC values, particularly during the first 45 minutes. The USP is at present considering a proposal to amend the USP dissolution test for Carbamazepine Tablets to include a measurement at 15 min (Q between 40% and 70%) in addition to the measurement at 60 minutes (Q not less than 75%) in order to exclude products that have a very rapid or very slow dissolution rate and which might not be bioequivalent to Tegretol [4].

Following the successful multinational studies of the quality of glibenclamide [5] and prednisone tablet [6] formulations, in 1991 and 1992 respectively, conducted under the auspices of the Official Laboratories and Medicines Control Services (OLMCS) Section of FIP, a proposal to conduct a similar interlaboratory study of the quality of carbamazepine 200mg tablet (conventional-release) products was adopted by the OLMCS at the 1992 FIP Congress in Lyon. The adoption of carbamazepine products as the candidate for the study was based on concerns over possible bioinequivalence among generic carbamazepine products and the innovator's product Tegretol (Ciba-Geigy) [7,8].

The principal aim of the multinational study was to obtain information about the quality of carbamazepine tablet formulations (200 mg) on the markets of the participating countries, with particular emphasis on *in vitro* release profiles. The information

generated should be useful in evaluating the interchangeability of products from different countries, e.g. within the European Union, and in evaluating the proposal to include an additional time point in the USP dissolution test.

EXPERIMENTAL

Protocol

The study protocol, which was prepared by the Medicines Testing Laboratory, Edinburgh, was distributed among potential participants for comment and adopted at the FIP Congress in September 1992.

Samples

Participants were asked to test either one or (preferably) two different batches of each brand of 200mg carbamazepine tablets (conventional-release) marketed in their own countries.

Standard sample

Approximately 75 Tegretol Tablets 200mg from a single batch (142900), provided by Ciba-Geigy, Basle, Switzerland, were supplied to each participating laboratory.

Test methods

The protocol comprised the following instructions which were sent to participating laboratories.

A. Ph. Eur. monograph for Tablets (Compressi, 1990, 478).

1. Disintegration. Record the maximum disintegration time of 6 tablets. (All laboratories were requested to determine disintegration time to investigate if a correlation between dissolution and disintegration times exists).
2. Uniformity of Mass. Record the average mass and the percentage deviation in the form, -x% to +y% of the average mass. State whether the sample complies with the Ph. Eur. requirements.

B. BP (1988) monograph for Carbamazepine Tablets.

1. Identification
   a) Melting point. Record the melting point.
   b) Colour reaction. Record whether sample complies.
   c) Fluorescence. Record whether sample complies.
2. Related substances. Record whether sample complies.
3. Assay. Record the result of the assay.

The protocol allowed the substitution of the tests in the European and British Pharmacopoeia monographs by those of the United States Pharmacopeia XXII (7th Supplement) in those countries in which the standards of the USP are preferred.

C. USP XXII dissolution test for Carbamazepine Tablets. (Seventh Supplement USP-NF).

Apparatus	:	USP XXII apparatus 2 at 75 rpm
Medium	:	Water containing 1% sodium lauryl sulphate (>98% pure by acidimetric titration); 900ml
Times	:	(5,10), 15, 30, 45, 60, 90, 120, (180) minutes. [The optional 5 and 10 minute time points were included for fast releasing (>50% in 15 min) products and the 180 minute time point was included to ensure complete (>95%) release of slower releasing products. Later time points could be omitted if complete (>95%) dissolution occurred in a shorter period].
Analysis	:	Spectrophotometric measurement at 288 nm after appropriate dilution if a 1cm cell is used. Alternatively, a shorter pathlength cell for undiluted samples could be used. 5-ml aliquots were removed at each time point and replaced by test medium, if possible. Alternatively, correction for the volume change in the calculation was allowed.
Reference solution	:	Solution of carbamazepine, at an appropriate concentration, in test medium containing not more than 1% of methanol. (A chemical reference standard of assigned purity was required, e.g. Carbamazepine USP Reference Standard).
Number of tablets	:	6 tablets per sample.
Calibration:		The apparatus should have been recently calibrated by using USP Official Reference Standard Prednisone Tablets (Dissolution calibrator, disintegrating), available from USP or local agents.

RESULTS AND DISCUSSION

Participating Laboratories and Products Tested

Twenty-two laboratories in nineteen countries took part in the study and results on 86 samples representing at least 34 different products were submitted. 30 different samples of Tegretol (28 different batches), 13 other branded products and 20 generic brands were tested.

The list of participants is shown in Table 1 and the products tested are shown in Table 2. The identity of the products tested in Canada, Spain and the United Kingdom are not disclosed at the request of the National Authorities.

Results of the Multinational Survey

Table 3 shows the number of brands, number of batches, the range of melting point temperatures in the identification test, the range of results in the test for uniformity of mass as a percentage deviation from the average mass, the maximum disintegration time, the range of percent dissolved at 15 and 60 minutes and the range of assay results.

All the results for the melting point in the identification test fell within a narrow range of 189.5°C to 192°C, except those from Mexico which reported values in the range 180° - 182°. No negative identifications in any of the three identification tests were recorded.

Compliance in the test for uniformity of mass was reported for all batches except for one batch in Germany.

The disintegration times ranged from 0.3 to 16 min. The latter value (from Mexico) is outside of the Ph. Eur. limit of 15 minutes for Uncoated Tablets (there is no disintegration requirement for Carbamazepine Tablets in the USP). There was not a rectilinear relationship between the disintegration times and the % dissolved at 15 min and 30 min. However, it was noted that the two samples with a disintegration time of more than 10 min had slower dissolution and had released only 5.4% and 31.7% after 15 min (12.3% and 69.1% after 30 min; 25.8% and 85.1% after 60 min respectively).

In the assay, four countries reported slightly low results, outside of the ±5% of declared content requirement of the BP. However, two batches (from Spain), giving assay results of 93.7% and 94.5% respectively, by the USP HPLC method, complied with the ±8% limits of the USP. One batch in Luxembourg gave a value of 94.3% by the ultraviolet spectrophotometric assay of the BP but a value of 99.4% by HPLC. One batch from Mexico giving a value of 94.5% complied with the USP requirement. A batch from the UK,

TABLE 1: Names of the Institutions and Principal Investigators of the Participating Countries.

Country	Institution	Investigators
Austria	Institut fur Pharmazeutische Technologie,University of Vienna	H. Viernstein
Canada	Banting Research Centre, Health Canada, Ottawa	I.J. McGilveray, S.A. Qureshi
Cyprus	State General Laboratory, Nicosia	M. Aletrari
Denmark	National Board of Health, Medicines Division, Bronshoj	M. Handlos
Finland	National Agency for Medicines, Helsinki	E. Totterman
France	Faculty of Pharmacy, University of Clermont-Ferrand	J.-M. Aiache
Germany	Zentrallaboratorium Deutscher Apotheker, Eschborn	H. Blume, S.L. Ali, J. Kraemer
Greece	Aristotelion University of Thessaloniki, Department of Pharmacy, Thessaloniki	M. Georgarakis
Luxembourg	Laboratoire National de Sante, Division Chimie Toxicologique et Pharmaceutique	J.-L. Robert
Mexico	Universidad Nacional Autonoma de Mexico	Helgi Jung C.
Netherlands	Laboratorium der Nederlandse Apothekers, S-Gravenhage Controle Laboratorium voor Nederlandse Apotheekhoudende Geneeskundigen, Zaandam. Rijksinstituut voor Geneesmiddelenenonderzoek, Leiden	O.S.N.M. Smeets O.M. van Berkel-Geldof J. Nienhuis
New Zealand	Institute of Environmental Science and Research	R.A. Richardson
Portugal	Laboratorio de farmaceuticos, Lisboa	A. Farinha

TABLE 1: (Continued)

Names of the Institutions and Principal Investigators of the Participating Countries

Country	Institution	Investigators
Singapore	Institute of Science and Forensic Medicine	Woo Soo On
Spain	Minesterio de Sanidad y Consumo, Madrid	A. Velazquez
Sweden	Lakemedelsverket, Medical Products Agency, Division of Pharmacy, Uppsala Apoteksbolaget, Stockholm	J.-O. Waltersson H. Selander
Switzerland	Interkantonale Kontrollstelle fur Heilmittel, Bern	S. Steiner
United Kingdom	Medicines Testing Laboratory, Edinburgh Medicines Control Agency, London	A.G. Davidson R.G. Alexander
USA	FDA, Center for Drug Evaluation and Research, St. Louis, Missouri	H.D. Drew

that gave an assay result of less than 95% declared content, was a product whose product licence had been withdrawn in the UK.

Dissolution Profiles

The ranges of the mean % dissolved at 15 min and 60 min for products from each country are shown in Table 3, the individual profiles are shown in Fig. 1 and the overlaid profiles of all samples are shown in Fig. 2.

While the dissolution profiles of the batches within many individual countries were similar, some countries had brands with dissimilar dissolution profiles. This is particularly true of Finland, Canada, Germany, The Netherlands, Sweden, Denmark and Switzerland. It was noted that many of the samples that displayed the fastest dissolution rate were all from the same manufacturer in Finland.

Fig. 2 shows that large differences exist among products throughout the world. It is likely that the products at the

TABLE 2: Products Tested.

Country	Sample Name	Manufacturer	Batch No.
Austria	Tegretol	Ciba Geigy	2071
	Tegretol	Ciba Geigy	2193
	Neurotop	Gerot	1548291
Canada	Product A	-	-
	Product B	-	-
	Product C	-	-
Cyprus	Storilat 200	Remedica	5459
	Taver 200	Medochemie	61142
Denmark	Tegretol	Ciba Geigy	115500
	Tegretol	Ciba Geigy	132800
	Nordotol	Orion Farmos	SCA71B
	Karbamazepin "DAK"	Nycomed DAK	L306150
	Karbamazepin "NM"	Gerard Lab	106055B
	Tegretol (Paranova)	Ciba Geigy	134700-2
Finland	Tegretol	Ciba Geigy	135100
	Tegretol	Ciba Geigy	125300
	Neurotol	Orion	SCA02C
	Neurotol	Orion	SFA050
France	Tegretol	Ciba Geigy	140100
	Tegretol	Ciba Geigy	119800
Germany	Tegretol	Ciba Geigy	345
	Tegretol	Ciba Geigy	319
	Sirtal	Sanofi Pharma	10621
	Sirtal	Sanofi Pharma	20803
	Fokalepsin	Promonta	292002
	Timonil	Desitin Arzneimittel	325072
Greece	Tegretol	Ciba Geigy	371092
	Tegretol	Ciba Geigy	383692
Luxembourg	Tegretol	Ciba Geigy	131100
	Tegretol	Ciba Geigy	134000

TABLE 2 (Continued) : Products Tested

Country	Sample Name	Manufacturer	Batch No.
Mexico	Tegretol	Ciba Geigy	30114
	Tegretol	Ciba Geigy	20912
	Carbazina	Psicofarma	2130193
	Carbazina	Psicofarma	1920992
	Neugeron	Armstrong	B306820
	Neugeron	Armstrong	M206632
Netherlands	Tegretol	Ciba Geigy	131100
	Carbamazepinum	Pharmachemie	91G30MC
	Carbamazepinum	Centrafarm	92E18A
	Carbamazepinum	Genfarma	91H18/ 0107111
	Carbymal	Katwijk Farma	88C14A
	Carbamazepinum	Pharbita	073I21
	Carbamazepine	Farmaver	FV920328
	Carbamazepine	Sudco	90D06-1
	Carbamazepine	Stephim	920506
New Zealand	Tegretol	Ciba Geigy	133100
	Teril	Pacific	K7705
Portugal	Tegretol	Ciba Geigy	414351
	Tegretol	Ciba Geigy	416814
Singapore	Mazetol	-	2V1393
	Mazetol	-	2U1226
	APO Carba-mazepine	-	V2091
Spain	Brand A	-	-
	Brand B	-	-
Sweden (Apoteksbolaget)	Tegretol	Ciba Geigy	115600
	Tegretol	Ciba Geigy	136100
	Hermolepsin	Orion Farmos	SAA01A
	Hermolepsin	Orion Farmos	SFA07B
Sweden (Medical Products Agency)	Tegretol	Ciba Geigy	115500
	Tegretol	Ciba Geigy	133000
	Hermolepsin	Orion	SFA07A
	Karbamazepin	Gerard Labs	20606

(continued)

TABLE 2 (Continued) : Products tested

Country	Sample Name	Manufacturer	Batch No.
Switzerland	Tegretol	Ciba Geigy	136300
	Tegretol	Ciba Geigy	133100
	Timonil	Desitin Arzneimittel	314100
	Timonil	Desitin Arzneimittel	277069U
	Carzetol	Sanofi	10683
	Carzetol	Sanofi	20813
UK	Product A	-	-
	Product A	-	-
	Product B	-	-
	Product B	-	-
	Product C	-	-
	Product C	-	-
	Product C	-	-
	Product D	-	-
	Product D	-	-
	Product E	-	-
	Product F	-	-
	Product F	-	-
USA	Carbamazepine	Qualitest	1122909
	Carbamazepine	Lemmon Co.	109322
	Carbamazepine	Purepac	079L2
	Carbamazepine	Rugby Labs.	109248
	Carbamazepine	Schein	109244

extremes of the dissolution rates are not bioequivalent. However, there is insufficient information available to determine the *in vitro* limits that will ensure bioequivalence. These limits can be determined only in conjunction with bioavailability studies.

USP *in vitro* limits

Detailed examination of the percentage dissolved from the six individual tablets of each of the 86 samples that were tested shows that 26 samples (30% of the total) failed to comply with the S_1 criterion of the USP (not less than 80% of the labelled amount of carbamazepine is dissolved from each tablet). Of the 26 samples

that failed this requirement, 13 were Tegretol samples (43% of all the Tegretol samples).

The standard sample of Tegretol failed to comply with the S_1 criterion when tested in six laboratories: two laboratories reported at least one unit less than 60% dissolved which would result in the sample failing the stage 2 criterion also.

There was no requirement in the protocol to test beyond stage 1 by testing additional tablets. It is likely that most of the samples would comply at stage 2 if similar results in the second series of six tablets to those in the six tablets tested were obtained. Indeed, this was proved to be the case in three countries that did perform repeat testing to stage 2. However, one generic sample from The Netherlands with individual tablet results of less than 50% (Q-25%) at 60 min would fail the USP requirement for dissolution even at stage 3. Thus, of the 86 samples examined in the survey, only one sample, from The Netherlands, is known with certainty to fail the USP requirement for dissolution.

When assessed against the proposed requirement at the additional 15 minute testing interval in the USP monograph (every unit should be between 40% and 70% dissolved), 71 samples (81%) failed and of the Tegretol samples, 18 (60%) failed. Since two of the three Canadian samples, 6 of the 7 Mexican samples and 5 of the 6 samples from the USA failed the requirement, it is recommended that further consideration is given to the requirement at the proposed additional testing interval at 15 min in the USP monograph.

Many of the failures resulted from the proposed requirement that *all* tablets are 40 - 70% dissolved at 15 min and it may be more appropriate for the purpose of this test to apply limits based on a mean (of the 6 tablets) and wider limits for the individual tablets. For example, accept if the mean value at 15 min is between 40% and 80% and no individual value is outside of the range 35 - 85%. These limits would still exclude 1 Canadian, 1 Cypriot, 2 Danish, 1 French, 1 German, 1 Luxembourg, 1 Mexican, 3 Dutch, 3 Swedish, 1 Swiss and 5 UK samples, including all the samples known to be from the Finnish manufacturer.

Standard Sample Results

The standard sample was analysed in 20 laboratories although not all the tests were carried out in all laboratories. The results are shown in Table 4.

The results for disintegration (all values 1 min or less), average tablet mass (279 mg; range 278 - 280.4 mg), uniformity of mass, -(0.7 - 2.2)% to +(0.6 - 2.9)%, were very similar in all

TABLE 3

Results of the Multinational Survey of Carbamazepine Products

Country	Brands (Batches)	Identification	Melting Point °C	Uniformity of mass (%) +	Uniformity of mass (%) -	Maximum Disintegration Time (minutes)	Dissolution (%) 15 min	Dissolution (%) 60 min	Assay (%)
Austria	2 (3)	+	189.8 - 190.3	4.8	6.0	4.5	70-78	93-99	96.4 - 99.0
Canada	3					0.3	54-86	75-99	97.4 - 100.1
Cyprus	2 (2)	+	190.8 - 190.9	1.5	1.6	5	69-77	96-97	98.7 - 99.0
Denmark	4 (6)	+	190.8 - 191.5	3.5	2.6	3.5	66-99	87-97	96.3 - 101.2
Finland	2 (4)	+	189.5 - 191.0	4.9	2.5	6.5	68-99	99-104	98.4 - 100.0
France	1 (2)							35-67	54-88
Germany	4 (6)	+	191 - 192	2.7	9.0	6.5	22-76	72-97	101.2 - 104.7
Greece	1 (2)	+	191.1 - 191.7	1.6	3.5		52-59	82-88	98.5 - 99.0
Luxembourg	1 (2)	+	191.1 - 191.7	1.6	3.5	0.8	75-80	100	94.3 - 97.8 (UV) 98.3 - 99.4 (HPLC)
Mexico	3 (6)		180 - 182			16	32-82	71-93	94.5 - 102.1

Netherlands	9 (9)			(rsd = 1.8%)		14	5.4-96	26-100	96 - 100
New Zealand	2 (2)	+	190.3	1.6	2.5	0.4	68-72	95-99	98.5 - 100.5
Portugal	1 (2)			3.3	3.2	0.75	62-67	71-84	96.1 - 100.3
Singapore	2 (3)	+	189.9 - 191.6	3.2	7.9	0.75	50-87	74-105	99.0 - 102.2
Spain	(2)					0.6	50-55	81-82	93.7 - 94.5
Sweden (Apoteksbolaget)	2 (4)	+	191 - 192	4.1	4.9	4	67-100	91-100	98.3 - 101.7
Sweden (Medical Products Agency)	3 (4)			3.9	2.9	4	63-99	92-103	99.6 - 102.3
Switzerland	3 (6)	+	190.8 - 191.4	2.5	2.1	3	38-79	61-96	99 - 101
United Kingdom	6 (12)	+	190 - 191	4.9	3.7	9	44-102	84-101	93.4 - 101.4
USA	5 (6)						73-83	89-98	100.2 - 104.4

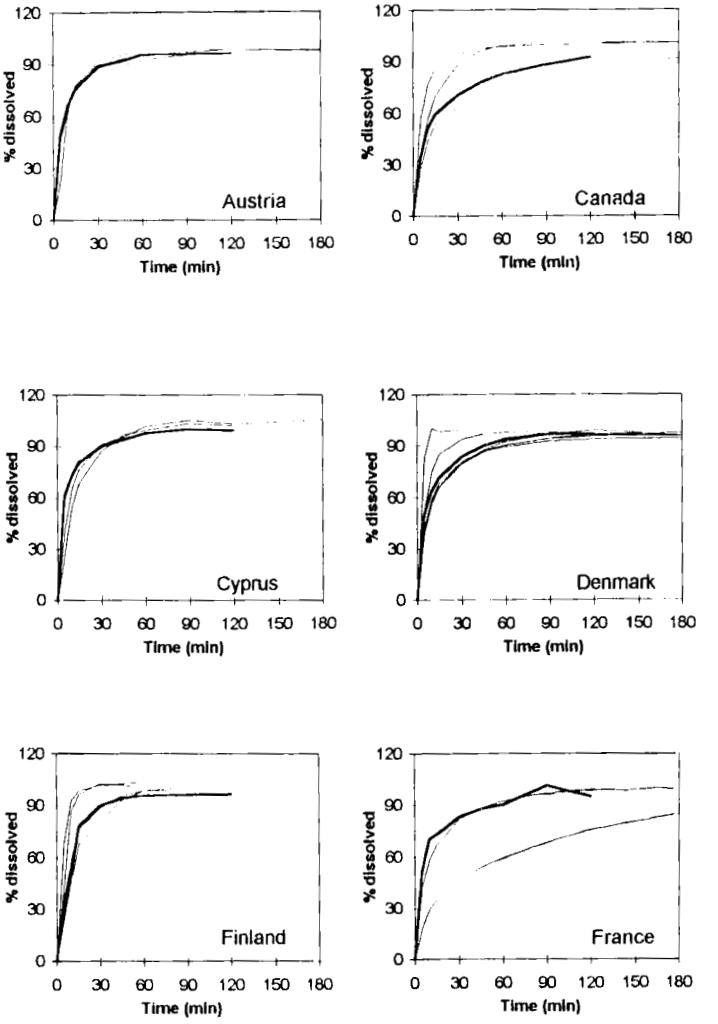

FIGURE 1

Dissolution profiles of carbamazepine tablets (200 mg) from 19 individual countries. (The bold line is the profile for the standard sample of Tegretol Tablets)

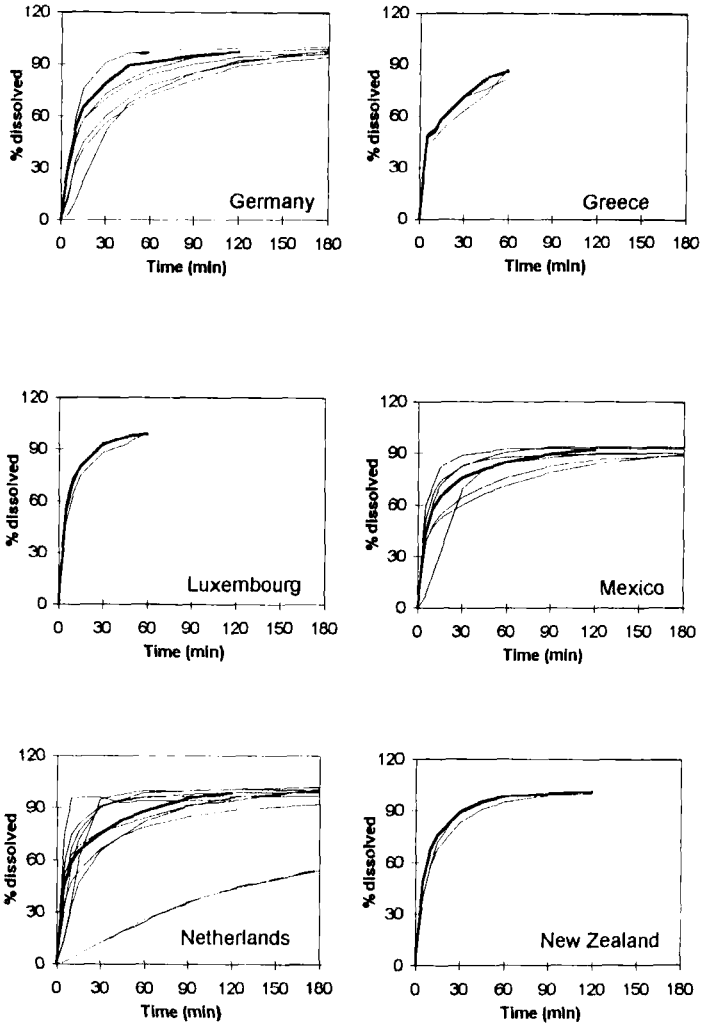

FIGURE 1, CONTINUED

Dissolution profiles of carbamazepine tablets (200 mg) from 19 individual countries. (The bold line is the profile for the standard sample of Tegretol Tablets)

(continued)

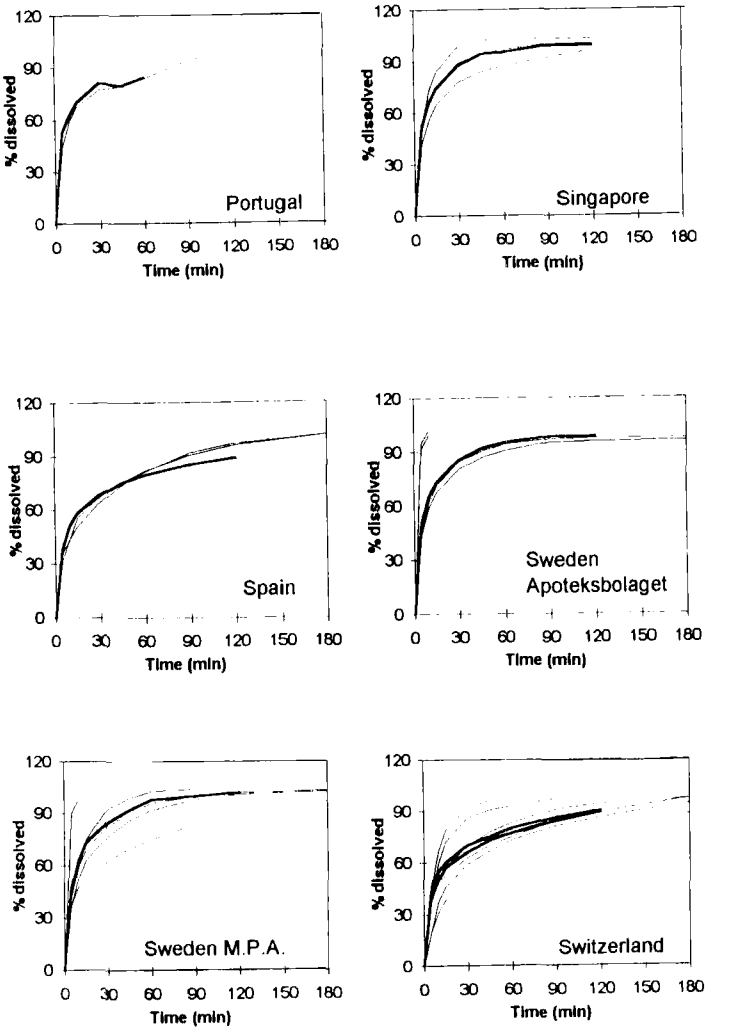

FIGURE 1, CONTINUED

Dissolution profiles of carbamazepine tablets (200 mg) from 19 individual countries. (The bold line is the profile for the standard sample of Tegretol Tablets)

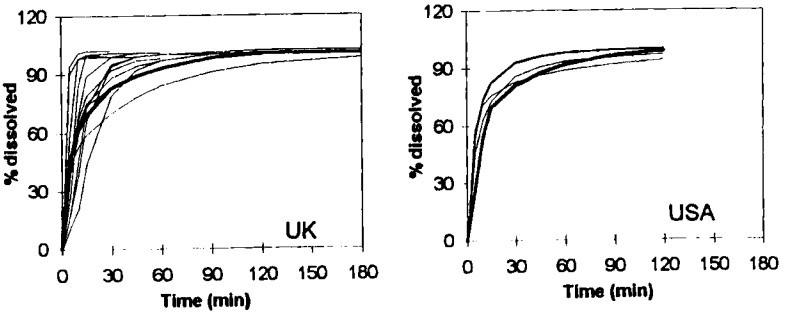

FIGURE 1, CONTINUED

Dissolution profiles of carbamazepine tablets (200 mg) from 19 individual countries. (The bold line is the profile for the standard sample of Tegretol Tablets)

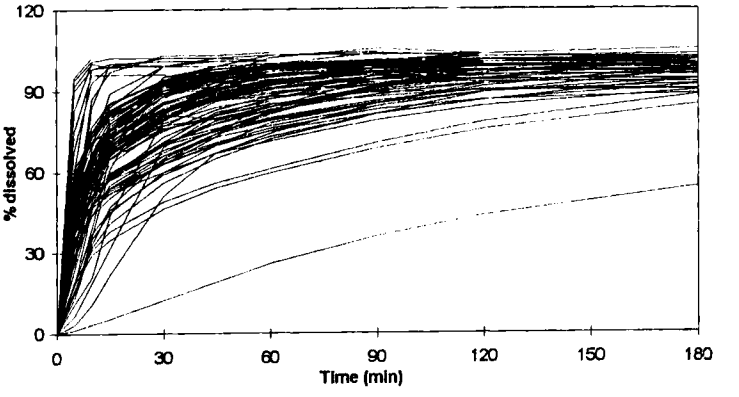

FIGURE 2

Dissolution profiles from the 19 countries (all results)

TABLE 4 Results for Carbamazepine Standard Sample

Identification (melting point)	-	**181° - 191° (n=11)**
Average Tablet Mass	-	**279 mg (278 - 280.4 mg) (n=13)**
Uniformity of Mass	-	**-(0.7 - 2.2)% to +(0.6 - 2.9)% (n=13)**
Disintegration	**All 1 *min* or less (n=16)**	

Assay

All results	**(UV or HPLC)**	**98.2% ±3.6% (n=18)**
	UV	**97.9% ±3.7% (n= 8)**
	HPLC	**97.6% ±5.2% (n= 4)**

Dissolution (n=20)

	% Dissolved			
	15 min	**30 min**	**45 min**	**60 min**
mean	**70**	**81**	**87**	**91**
range	**58 - 81**	**68 - 93**	**74 - 97**	**77 - 99**

laboratories. No negative identifications were reported although Mexico reported a melting point of 181°C (*cf.* the BP requirement of about 191°C).

The assay results (by both UV and HPLC) gave a mean value of 98.2 ±3.6 (sd)% (n=18). The results for the UV assay method of the British Pharmacopoeia and HPLC assay of the USP (where the method used was indicated) were 97.9 ±3.7% (n=8) and 97.6 ±5.2% (n=4) respectively.

The mean values for percent dissolved at 15, 30, 45 and 60 min are also shown in Table 4 and the dissolution profiles are shown in Fig. 3. At each of the time points the results reported by a number of laboratories were outside the range of ±10%

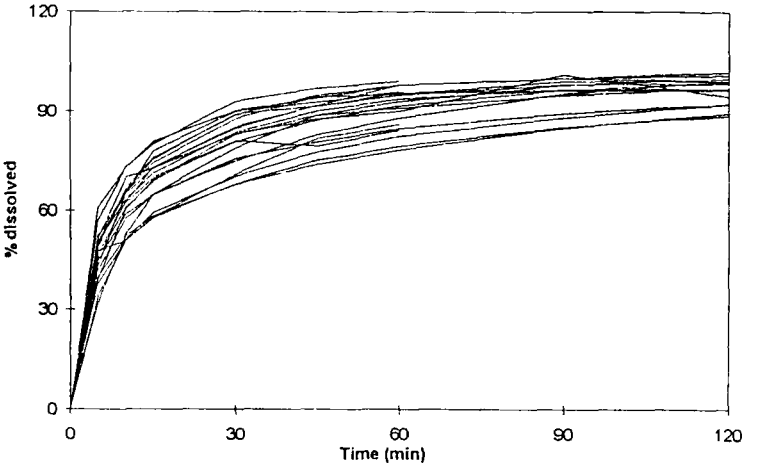

Figure 3

Dissolution profiles of a standard sample of carbamazepine tablets (200mg) tested in 20 laboratories.

(calculated with reference to the label content) of the mean values (n=20). A range of ±10% of mean value from all laboratories for percent dissolved from the standard sample has been adopted as the criterion for inclusion of the results of tests on samples in previous reports of OLMCS multinational surveys [5,6]. However, subsequent statistical analysis of data on the standard sample and on the USP Prednisone Calibrator Tablets by S.A. Qureshi and I.J. McGilveray (Canada) showed that inter-laboratory percent drug release values were comparable for both the prednisone calibrator and the standard sample and that within-a-dissolution run relative standard deviation values appeared to be larger for the standard sample than for the calibrator [9]. Consequently, all submitted data on samples have been included in the report (in one case after re-analysis of the standard sample and marketed products).

ACKNOWLEDGEMENTS

The author thanks all the investigators for the data used in the compilation of this report and grateful acknowledgement is made of the statistical evaluation conducted by I.J. McGilveray and S.A. Qureshi, Canada.

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