DRUG DEVELOPMENT AND INDUSTRIAL PHARMACY, 19(20), 2713-2741 (1993)

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PHARMACEUTICAL QUALITY OF GLIBENCLAMIDE PRODUCTS A MULTINATIONAL POSTMARKET COMPARATIVE STUDY

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SUMMARY

A multinational postmarket comparative study of pharmaceutical quality of glibenclamide products was performed in cooperation with large number of laboratories and under anspices of the Section of Official Laboratories and Medicines Control Services of FIP and World Health Organization. 28 countries from Europe, Africa, North and South America, Asia and Australia participated in this study. Altogether 142 glibenclamide tablet formulations of the respective countries were investigated. The products were tested for identity, purity, content, uniformity of content and in-vitro dissolution properties. Most products tested fulfilled the pharmacoepial requirements concerning identity, purity and content (95 - 115 %). Marked differences were recorded in respect of in-vitro dissolution behaviour. This applies not only to the products of different countries but also among products of the same country. It is anticipated that

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products, which are markedly differenticated in their in-vitro dissolution properties, exhibit therapeutically relevant differences in bioavailability.

INTRODUCTION

Sulfonylureas are the most important group of oral antidiabetic drugs. First marketed compounds of this group were carbutamide and tolbutamide. Through further molecular variations a second generation of compounds was developed which are equally effective in much lower doses. Among these compounds glibenclamide (brand names: Euglucon and Daonil) is one of widely sold oral antidiabetic drug in Europe and an important agent in North America.

After expiry of the innovator's patent in July 1983 large numbers of generic preparations were introduced in the market within few weeks. As a consequence, at present many generic versions of Euglucon/Daonil are available on the market in European countries as well as worldwide.

In May 1982 the innovator compony had introduced in Germany a 3.5/1.75 mg micronised glibenclamide formulation as brand "Euglucon N" to substitute the old 5.0/2.5 mg "Euglucon" version. Subsequently most of the generics in Germany also switched over to this dosage strength. However this new formulation of 3.5 mg strength is now also available in other European countries like Switzerland, Luxemburg, Sweden and Finland.

In the past decade several comparative studies [1 - 6] on the pharmaceutical quality of glibenclamide formulations of the German market were performed by Zentrallaboratorium Deutscher Apotheker (ZLDA). Marked differences in quality, particularly concerning in-vitro dissolution properties, were detected among various products. Subsequent bioavailibility and pharmacodynamic (including measurements of serum insuline and C-peptide as well as blood glucose levels) studies with these formulations confirmed differences of therapeutic relevance between the product.

Aim of this multinational postmarket comparative study was the in-vitro quality control of glibenclamide formulations marketed in different countries. In view

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of the realisation of the European Community all EC member states except Ireland were included. Altogether 28 countries participated in the study. In Table 1 the names of countries, the number of glibenclamide tablet formulations marketed there as well as the names of all participating institutions and investigators are listed.

Study protocol was prepared by ZLDA basing on the pharmacopeial requirements as well as the state of the art in pharmaceutical sciences. The protocol was distributed to all participants, subsequently discussed during the spring meeting of the FIP Section of Official Laboratories and Medicines Control Services (OLMCS) in May 1990 in Eschborn, Germany and finally approved by all participants and investigators. Experiments were performed in accordance to the study protocol in all laboratories.

Identity, purity, content and uniformity of content were tested according to the monograph "Glibenclamide Tablets" of British Pharmacopeia 1988. Furthermore, disintegration and in-vitro dissolution were analysed in accordance to the study protocol. Euglucon 5 mg tablets were used as calibrator reference for the dissolution experiments. These tablets were supplied to all study participants by the coordinators of the study.

MATERIALS AND METHODS

All glibenclamide products (1.75, 2.5, 3.5 or 5.0 mg strengths), whichever marketed in the respective countries, were included in the study. Samples of one batch each were purchased from the market (retail pharmacy or wholesaler). Additionally samples of a second batch — if available — were procured directly from the manufacturers (or also from pharmacies) and included in the study.

Tests for identification (TLC, light absorption in the range from 230 nm to 350 nm) and related substances (maximum 2.4/0.4 %) were performed with BP reference standards according to BP '88. Content and uniformity of content were determined spectrophotometrically at 300 nm or using an alternate specific HPLC method [2]. Test for disintegration was performed with 6 tablets with the apparatus of European Pharmacopeia. In-vitro dissolution was tested in USP

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TABLE 1: Participating Countries and Products tested

Name of the product	Strength	Batch No.	Expiry date	Manufacturer
Argentina				
1) Daonil	5.0 mg	DWC	---	Hoechst
	5.0 mg	DAW	---	Hoechst
2) Diabemin	5.0 mg	010117	---	Ingram
	5.0 mg	090424	---	Ingram
3) Euglucon	5.0 mg	811-041-11	---	Boehringer Arg.
	5.0 mg	831-055-11	---	Boehringer Arg.
4) Pira	5.0 mg	7020	---	Omega
	5.0 mg	7022	---	Omega
Australia				
1) Daonil	5.0 mg	28034 4	12/92	Hoechst Australia Ldt.
	5.0 mg	28298 1	04/95	Hoechst Australia Ldt.
2) Euglucon	5.0 mg	747086-01	10/94	Boehringer Mannheim
	5.0 mg	747418-04	01/95	Boehringer Mannheim
3) Glimel	5.0 mg	H5503C	04/93	Alphapharm Pty. Ltd.
	5.0 mg	G0603A	05/92	Alpharpharm Pty. Ltd.
Austria				
1) Dia-Eptal	3.5 mg	801037	---	Montavit
2) Euglucon	5.0 mg	02461	---	Boehringer Mannheim
	5.0 mg	02561	---	Boehringer Mannheim
	5.0 mg	48525	---	Boehringer Mannheim
3) Euglucon	5.0 mg	10H129	---	Hoechst

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TABLE 1: (continued)

Name of the product	Strength	Batch No.	Expiry date	Manufacturer
Austria continued				
4) Gewaglucon	5.0 mg	294531	---	Heilmittelwert Wien
	5.0 mg	294541	---	Heilmittelwert Wien
5) Glibenclamid	3.5 mg	472400	---	Genericon
6) Glucobene	1.75 mg	0003C0	---	Merckle
	1.75 mg	0655A0	---	Merckle
	3.5 mg	0645IO	---	Merckle
	3.5 mg	0645HO	---	Merckle
7) Normoglucon	1.75 mg	47180A	---	Klinge Pharma
	3.5 mg	59189P	---	Klinge Pharma
	5.0 mg	59188P	---	Klinge Pharma
8) Semi-Euglucon	1.75 mg	742673/2	---	Boehringer Mannheim
	1.75 mg	527 CO 24	---	Hoechst
Belgium				
1) Daonil	5.0 mg	143H611	March 95	Hoechst AG
2) Euglucon	5.0 mg	90D05 (746101-03)	April 95	Boehringer Mannheim
Canada 1				
1) Glibenclamide	5.0 mg	A	09/93	A*)
2) Glibenclamide	5.0 mg	BB	07/93	A*) (local Pharmacy)
3) Glibenclamide	5.0 mg	CC	04/93	B*)
4) Glibenclamide	5.0 mg	DD	01/93	B*) (local Pharmacy)

* Names not disclosed

(continued)

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TABLE 1: (continued)

Name of the product	Strength	Batch No.	Expiry date	Manufacturer
Canada 2				
1) Glyburide	2.5 mg	A1	---	A*)
2) Glyburide	2.5 mg	A2	---	A*)
3) Glyburide	2.5 mg	B1	---	A*)
4) Glyburide	2.5 mg	C1	---	A*)
5) Glyburide	5.0 mg	A3	---	A*)
6) Glyburide	5.0 mg	A4	---	A*)
7) Glyburide	5.0 mg	B2	---	A*)
8) Glyburide	5.0 mg	C3	---	A*)
9) Euglucon	5.0 mg	48525	---	Boehringer
Canada 3				
2) Albert Glyberide	5.0 mg	5352 A	---	B*)
	5.0 mg	5342 A	---	B*)
1) Diabeta	5.0 mg	6047 A	---	A*)
	5.0 mg	5960 A	---	A*)
Chile				
1) A1*)	5.0 mg	---	---	B*)
2) A2*)	5.0 mg	---	---	B*)
3) B1*)	5.0 mg	---	---	B*)
4) B2*)	5.0 mg	---	---	B*)
5) C1*)	5.0 mg	---	---	B*)
6) C2*)	5.0 mg	---	---	B*)
7) D1*)	5.0 mg	---	---	B*)
8) D2*)	5.0 mg	---	---	B*)

* Names not disclosed

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TABLE 1: (continued)

Name of the product	Strength	Batch No.	Expiry date	Manufacturer
Chile continued				
9) E1 *)	5.0 mg	---	---	B *)
10) E2 *)	5.0 mg	---	---	B *)
11) F1 *)	5.0 mg	---	---	B *)
CIS				
1) Glibenklamidum Betanas	5.0 mg	C/796 A 59527	Aug 93	Cadila Lab
2) Maninil 5	5.0 mg	911088	---	VEB Arzneimittel, Dresden
Denmark				
1) Daonil	3.5 mg	a) 149 H 102	---	Hoechst AG
		b) 137 H 101	---	Hoechst AG
2) Euglucon	3.5 mg	a) PA 20017	---	Ercopharm
		b) PA 20019	Oct. 94	Ercopharm
3) Hexaglucon	3.5 mg	a) 118102	---	Durascan
		b) 6981	---	Durascan
Egypt				
1) A I *)	5.0 mg	---	11/95	Biochemical Industries
2) A II	5.0 mg	---	12/94	Biochemical Industries
3) B I	5.0 mg	---	11/93	Hoechst Orient
4) B II	5.0 mg	---	10/93	Hoechst Orient
5) B III	5.0 mg	---	04/94	Hoechst Orient
6) B IV	5.0 mg	---	08/92	Hoechst Orient
7) C I	5.0 mg	---	09/93	local made
8) C II	5.0 mg	---	03/94	local made

* Names not disclosed

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TABLE 1: (continued)

Name of the product	Strength	Batch No.	Expiry date	Manufacturer
Egypt continued				
9) C III	5.0 mg	---	11/94	local made
10) D I	5.0 mg	---	03/94	local made
11) D II	5.0 mg	---	08/93	local made
Finnland				
1) Daonil	3.5 mg	a) 92H100	April 93	Hoechst
		b) 149 H 102	May 93	Hoechst
2) Euglucon	3.5 mg	QH 5-1	Aug 93	Orion
3) Gilemid	5.0 mg	a) OK 8	Nov 91	Star, Huhtamäki
		b) 08187	Jan 93	OY Leiras
France				
1) Daonil	5.0 mg	---	---	Laboratoires Hoechst
2) Euglucon	5.0 mg	---	---	Laboratoires Pierre Fabre Medicament
3) Miglucon	2.5 mg	---	---	Laboratoires Pierre Fabre Medicament
Germany				
1) Azuglucon 3,5	3.5 mg	30308	Dec. 94	Azuchemie
2) Bastiverit	3.5 mg	80117	June 92	Bastian Werk
3) dia-basan	3.5 mg	801089	June 94	Sagitta
4) duraglucon N	3.5 mg	F 665	June 92	Durachemie
5) Euglucon N	3.5 mg	745382-02	Dec. 94	Boehringer Mannheim
6) Gliben-Puren N	3.5 mg	91003202	March 94	Klinge-Nattermann

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TABLE 1: (continued)

Name of the product	Strength	Batch No.	Expiry date	Manufacturer
Germany continued				
7) Glibenclamid 3.5 GDS	3.5 mg	108804	June 91	GDS Searle
8) Glibenclamid 3.5 Riker	3.5 mg	OB 46 251	Dez. 92	Kettelhack Riker
9) Glibenclamid ratiopharm	3.5 mg	096619	Dec. 93	ratiopharm
10) Glimidstada	3.5 mg	16	June 94	STADApharm
11) Gluconorm	3.5 mg	12602	June 89	Wolff
12) Gluco-Tablinen	3.5 mg	039029	---	Beiersdorf
13) Glukoreduct	3.5 mg	341099	---	Midy
14) Glukovital 3.5	3.5 mg	129020	June 94	Wolff
15) Glycolande N	5.0 mg	38	June 93	Delalande
16) Orabetic 3.5	3.5 mg	890203	---	Dorsch
17) Praeciglucon	3.5 mg	0373	June 93	Pfleger
Great Britain				
1) A*)	5.0 mg	---	---	T*)
2) B*)	5.0 mg	---	---	T*)
3) C*)	5.0 mg	---	---	T*)
4) D*)	5.0 mg	---	---	T*)
5) E*)	5.0 mg	---	---	T*)
6) F*)	5.0 mg	---	---	T*)
7) G*)	5.0 mg	---	---	T*)
8) H*)	5.0 mg	---	---	T*)
9) I*)	2.5 mg	---	---	T*)
10) X*)	2.5 mg	---	---	T*)
11) Z*)	2.5 mg	---	---	T*)

* Names not disclosed

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TABLE 1: (continued)

Name of the product	Strength	Batch No.	Expiry date	Manufacturer
Greece				
1) Daonil	5.0 mg	a) OD 21	June 95	Hoechst Hellas
		b) OD 31	July 95	Hoechst Hellas
3) Deroctyl	5.0 mg	a) 104	June 95	G.A. Pharmaceuticals
		b) 154	June 95	G.A. Pharmaceuticals
2) Euglykon	5.0 mg	a) 9920F9	Sep 94	Farmalex
		b) 0509G0	Oct 95	Farmalex
Hungary				
1) Euglucon	5.0 mg	D 4	Dec 94	Boehringer Mannheim S.A.
2) Gilemal	5.0 mg	6720790	---	Chinion Budapest
Indonesia				
1) Daonil	5.0 mg	101W011	---	Hoechst Indonesia
	5.0 mg	099W010	---	Hoechst Indonesia
2) Euglucon	5.0 mg	3334600	---	Phapros Indonesia
	5.0 mg	4334100	---	Phapros Indonesia
Italy				
1) Glibenclamide	5.0 mg	A	---	Pharmacy
2) Glibenclamide	5.0 mg	B	---	Manufacturer
Japan				
1) Daonil	2.5 mg	43H008	---	Hoechst Japan Ltd.
	2.5 mg	11W001	---	Hoechst Japan Ltd.
2) Euglucon	2.5 mg	LWL043F	---	Yamanouchi Pharmaceutical
	2.5 mg	NBL060F	---	Yamanouchi Pharmaceutical

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TABLE 1: (continued)

Name of the product	Strength	Batch No.	Expiry date	Manufacturer
Luxemburg				
1) Daonil	5.0 mg	143H611/90C05	March 95	Hoechst AG
2) Euglucon 5	5.0 mg	745501-07	---	Boehringer Mannheim
3) Glibenhexal	3.5 mg	1184	Dec 94	Hexal-Pharma
4) Glibenclamid-ratiopharm	3.5 mg	0315C0	June 94	Ratiopharm
Netherlands				
1) Daonil	5.0 mg	89L06607	Dec. 93	Hoechst AG
2) Euglucon	5.0 mg	89J18 (745014-03)	Oct 93	Boehringer Mannheim
3) Glibenclamide 5 mg	5.0 mg	89D07-4	April 92	Lepharma
4) Glibenclamide 5 mg	5.0 mg	182020901003	May 93	Pharbita
5) Glibenclamide 5 mg	5.0 mg	90F26/766	March 93	Dumex
6) Glibenclamide 5 mg	5.0 mg	890720	July 92	Farmaver
7) Glibenclamidum 2.5 mg	2.5 mg	90E10E	Jan 93	Centrafarm
8) Glibenclamidum 5 mg	5.0 mg	90F22A	May 93	Centrafarm
9) Glibenclamidum 5 mg	5.0 mg	89B25/0100895-5602	Feb 92	ACF-Chemiefarma
10) Hemi-Daonil	2.5 mg	89L0724	Dec 94	Hoechst AG
11) Semi-Euglucon	2.5 mg	88F14 (742673-67)	June 93	Boehringer Mannheim
Pakistan				
1) Daonil	5.0 mg	H 122	Nov 95	Hoechst Pakistan
2) Euglucon	5.0 mg	T 0276	Oct 95	Pakistan, Vitamin Products

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TABLE 1: (continued)

Name of the product	Strength	Batch No.	Expiry date	Manufacturer
Portugal				
1) Daonil	5.0 mg	a) 201772	Jan 95	Hoechst Portugesa SA
		b) 201782	Jan 95	Hoechst Portugesa SA
2) Euglucon	5.0 mg	a) 03001	---	Boehringer Mannheim/ Lab Iberfar
		b) 06003	---	Boehringer Mannheim/ Lab Iberfar
Spain				
1) Daonil	5.0 mg	a) D 6	April 95	Hoechst Iberia S.A.
		b) D 14	July 95	Hoechst Iberia S.A.
2) Euglucon 5	5.0 mg	a) D 4	March 95	Boehringer Mannheim S.A.
		b) D 8	July 95	Boehringer Mannheim S.A.
3) Norglicem 5	5.0 mg	a) C 8	Febr 94	Lab. A. Gamir, S.A.
		b) C 7	Febr 94	Lab. A. Gamir, S.A.
Sweden				
1) Daonil	3.5 mg	a) 132U273	---	Hoechst AG
		b) 173H358	---	Hoechst AG
2) Euglucon	3.5 mg	a) PL/745370.01	---	Boehringer Mannheim
		b) PL/745382-03	---	Boehringer Mannheim
3) Glibenclamid	3.5 mg	a) POB 001	---	Kabi Vitrum AG
		b) POF 002	---	Kabi Vitrum AG

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TABLE 1: (continued)

Name of the product	Strength	Batch No.	Expiry date	Manufacturer
Switzerland				
1) A*)	5.0 mg	a) 64813 G b) 65084FB	March 93 Nov 94	T*)
2) B*)	5.0 mg	a) 745013-11 G b) 745365-02 F	--- ---	U*)
3) C*)	5.0 mg	a) 444C607 G b) 281 H 617 F	--- ---	V*)
4) D*)	3.5 mg	a) 903020 G b) 801089 F	--- ---	X*)
Thailand				
1) 1 a*)	5.0 mg	---	---	Under licence
2) 1 b*)	5.0 mg	---	---	Under licence
3) 2 a*)	5.0 mg	---	---	local made
4) 2 b*)	5.0 mg	---	---	local made
5) 3 a*)	5.0 mg	---	---	local made
6) 3 b*)	5.0 mg	---	---	local made
Turkey				
1) Gliben	5.0 mg 5.0 mg	1A 007 OK 021	01/96 10/95	--- ---
USA				
1) Diabeta	5.0 mg	a) 0530800 b) 0520900	--- ---	Hoechst-Roussel Hoechst-Roussel
2) Micronase	5.0 mg	a) 649 XM b) 690 XM	--- ---	Upjohn Upjohn

* Names not disclosed

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TABLE 2: Names of the Institutions and Investigators of the participating Countries

EC Country	Institution	Investigators
1) **Belgium**	Zentrallaboratorium Deutscher Apotheker, Eschborn, FRG	S. L. Ali M. Siewert
2) **Denmark**	National Board of Health, Medicines Division, Bronshoj	P. Helboe
3) **France**	Faculty of Pharmacy University of Clermont-Ferrand	J. M. Aiache
4) **Germany**	Zentrallaboratorium Deutscher Apotheker, Eschborn	H. Blume, S. L. Ali, M. Siewert
5) **Greece**	Aristotelion University of Thessaloniki, Department of Pharmacy, Thessaloniki	M. Georgarakis
6) **Italy**	Instituto Superiore Di Sanita Roma	E. Cingolani
7) **Luxemburg**	Laboratoire National de Santé, Division Chimic Toxicologique et Pharmaceutique	J.-L. Robert
8) **Netherlands**	Laboratorium der Nederlandse Apothekers, S-Gravenhage	F. J. Van de Vaart
9) **Portugal**	Faculdade de Farmácia, Laboratório de Biofarmácia, Lisboa	A. Farinha J. Morais
10) **Spain**	Zentrallaboratorium Deutscher Apotheker, Eschborn, FRG	Miss Olga Cancio (Pama)
11) **United Kingdom**	British Pharmacopeia Commission, London Medicines Testing Laboratory, Edinburgh	R. C. Hutton A. G. Davidson

XXII apparatus II (paddle) with 900 ml of buffer solution pH 7.4 (68.05 g KH_2PO_4 anhydrous and 15.64 g NaOH in 10 l water) and agitating at 75 rpm. 5.0 ml samples were withdrawn after 10, 20, 30, 60, 90 and 120 min, filtered through a suitable filter unit (e. g. 30 μm teflon) and absorbance measured at 227 nm. Euglucon 5 mg tablets were used as "calibrator" and "standard" for the in-vitro dissolution testing equipment. Results of this test allow an appropriate comparison of data from all different laboratories participating in the study.

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TABLE 2: (continued)

Other Countries	Institution	Investigators
1) **Argentina**	Faculty of Pharmacy and Biochemistry, University Buenos Aires	L. Goyanes C. Bregni
2) **Australia**	Therapeutic Goods Administration, Woden	Mr. R. J. Prestridge
3) **Austria**	Institut für Pharmazeutische Technologie, University of Vienna	H. Vierenstein
4) **Canada**	Health and Welfare, Ottawa; Ministry of Health Ontaria; University of Saskatchewan	I. J. McGilveray, S. A. Qureshi, R. Brien S. I. Borst, D.K.Y. Gerecki, C. R. Coghlin
5) **Chile**	Department of Phamacy, Catholic University of Chile, Santiago	R. P. Reyes
6) **Egypt**	Faculty of Pharmacy, University of Alexandria	S. A. Khalil
7) **Finland**	Lääkelaboratorio, National Medicines Control Laboratory, Helsinki	A. Kaukinen
8) **Hungary**	WHO Collaborating Centre for Drug Information and Quality Assurance	I. Bayer
9) **Indonesia**	National Quality Control Lab. of Drug and Food, Ministry of Health, Jakarta	I. Koatma, A. Setiawati H. Tetrasari
10) **Japan**	National Institute of Hygienic Sciences, Tokyo	N. Aoyagi
11) **Pakistan**	Zentrallaboratorium Deutscher Apotheker, Eschborn, FRG	S. L. Ali M. Siewert
12) **Sweden**	Läkemedelsverket, Medical Products Agency Division of Pharmacy, Uppsala	J.-O. Waltersson M. Haraldsdóttir

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TABLE 2: (continued)

Other Countries	Institution	Investigators
13) **Switzerland**	Interkantonale Kontrollstelle für Heilmittel, Bern	U. Salzmann S. Steiner
14) **Thailand**	Drug Analysis Division, Bangkok	S. Sawasdiphab
15) **Turkey**	Central Institute of Hygiene, Ankara	T. Burat
16) **USA**	FDA, Center for Drug Evaluation and Research, St. Louis, Missouri	H. D. Drew
17) **CIS**	Faculty of Pharmacy of Moscow Medical Seteschenow Institute	S. A Listov
18) **International Organisation**	World Health Organisation, W.H.O. Geneva	A. Mechkovsky, Miss M. Schmid

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RESULTS AND DISCUSSION

All preparations investigated in this study fullfilled the requirements of the British Pharmacopoeia for identity and purity (related substances).

Experimental results of content and uniformity of content are listed in Table 3. In this Table only minimum and maximum values determined for different products of the particular countries are documented. British Pharmacopoeia (for glibenclamide tablets) as well as EC member states guidelines [7] allow a maximum deviation of $\pm$ 5 % for assay at the release of the tablets after production. Such requirements are not fullfilled by some products from Argentina (3), Egypt (1), Germany (1), Indonesia (1) and United Kingdom (2).

Requirements concerning uniformity of content were fullfilled by all products tested except one from Denmark which showed a slightly higher deviation (115.4 %). In this context all products were of high quality standard.

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TABLE 3: Results of Assay and Content Uniformity Investigations of Glibenclamide Tablets (minimum and maximum Values obtained for Batches and Products)

Country	Content	Uniformity of Content
Argentina	99.6 % - 108.0 %	90.0 % - 113.0 %
Australia	95.5 % - 103.0 %	98.5 % - 103.0 %
Austria	99.2 % - 100.2 %	96.7 % - 102.9 %
Belgium	100.1 % - 102.7 %	100.3 % - 106.5 %
Canada	97.3 % - 104.4 %	92.8 % - 110.9 %
Chile	95.9 % - 101.0 %	87.4 % - 103.7 %
Denmark	98.3 % - 102.3 %	98.3 % - 115.4 %
Egypt	95.3 % - 106.8 %	86.0 % - 114.0 %
Finland	99.4 % - 101.2 %	91.3 % - 108.7 %
Germany	96.5 % - 107.6 %	95.5 % - 112.1 %
Greece	102.5 % - 103.5 %	98.0 % - 115.0 %
Indonesia	95.5 % - 105.2 %	87.2 % - 109.9 %
Italy	101.2 %	96.4 % - 102.7 %
Japan	93.7 % - 102.0 %	89.2 % - 104.6 %
Luxemburg	96.8 % - 103.3 %	91.9 % - 106.3 %
Netherlands	96.0 % - 101.0 %	92.0 % - 106.0 %
Pakistan	96.6 % - 100.5 %	93.0 % - 114.0 %
Portugal	102.0 % - 103.2 %	98.6 % - 105.7 %
Spain	100.7 % - 103.8 %	94.8 % - 107.6 %
Sweden	97.1 % - 100.9 %	95.1 % - 105.7 %
Switzerland	98.6 % - 101.4 %	95.3 % - 103.0 %
Thailand	95.8 % - 99.0 %	91.5 % - 105.4 %
Turkey	95.5 % - 98.4 %	92.3 % - 96.9 %
United Kingdom	94.7 % - 106.2 %	92.5 % - 104.0 %
USA	95.1 %	
CIS	96.4 % - 99.5 %	96.3 % - 107.3 %

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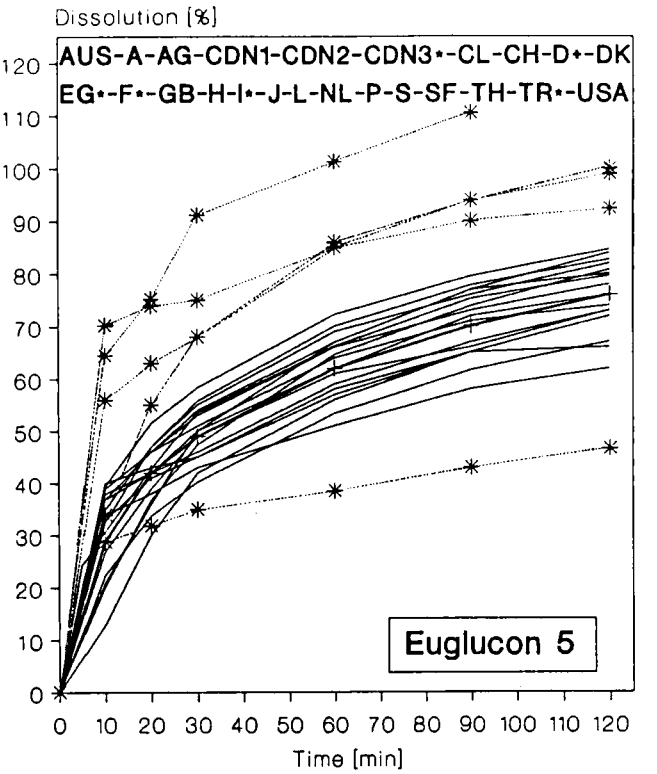

FIGURE 1:
Glibenclamide Comparative Study: Calibration of Dissolution Test

Legend for the alphabets of Figures 1 - 4

A	=	Austria	H	=	Hungary
AG	=	Argentine	I	=	Italy
AUS	=	Australia	ID	=	Indonesia
B	=	Belgium	J	=	Japan
CDN	=	Canada	L	=	Luxemburg
CH	=	Switzerland	NL	=	Netherlands
CL	=	Chile	P	=	Portugal
D	=	Germany	PK	=	Pakistan
DK	=	Denmark	S	=	Sweden
E	=	Spain	SF	=	Finland
EG	=	Egypt	SU	=	CIS
F	=	France	TH	=	Thailand
GB	=	United Kingdom	TR	=	Turkey
GR	=	Greece	USA	=	United States of America

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Results of in-vitro dissolution experiments are summarized in Figs. 1 - 4. Names (as far as disclosed), dosage strength, batch numbers, expiry dates and manufacturer of the products tested in the respective countries are listed in Table 1.

Dissolution profiles obtained with calibrator tablets in the different participating laboratories are shown in Fig. 1. It is obvious that in most cases very similar results were reported. However, in some cases deviating results were recorded, e. g. with a certain higher rate of dissolution.

Discussion of these results with all investigators revealed that higher dissolution curves could be caused by certain problems in the in-vitro dissolution system. Re-analyses of the calibrator tablets under slightly modified conditions verified this assumption. On the other hand outliers with lower curves could not be conclusively explained. On the basis of these findings inclusion and exclusion criteria for the in-vitro dissolution results of the individual laboratories were laid down by the participating investigators as following:

Results of a particular laboratory are reported in this publication only when the dissolution profiles of Euglucon 5 calibrator tablets investigated in that laboratory did not differ for more than ± 10 % from the "standard curve" (defined as the mean curve of a fivefold dissolution experiment of the calibrator tablets in ZLDA as reference laboratory). This "standard curve" (with green ink in Fig. 1) is almost superimposable with the median curve of all participating laboratories for the calibrator tablets. If the dissolution curve of the calibrator tablets investigated in a certain laboratory exhibits a more than ± 10 % deviation, then all results of glibenclamide tablets reported by this particular laboratory are not included in this paper. However, if the laboratory had sent samples of the products marketed in the particular country to ZLDA, they were cross-checked in the reference laboratory and the values thus obtained were included in this publication. This is the case for dissolution results of Canada 3, Greece, Indonesia, Italy and Turkey. In-vitro dissolution results of products from Egypt are not included at all in this publication, because the calibrator tablets profiles deviated for more than ± 10 % and the respective products marketed in Egypt were not submitted to ZLDA for cross-checking.

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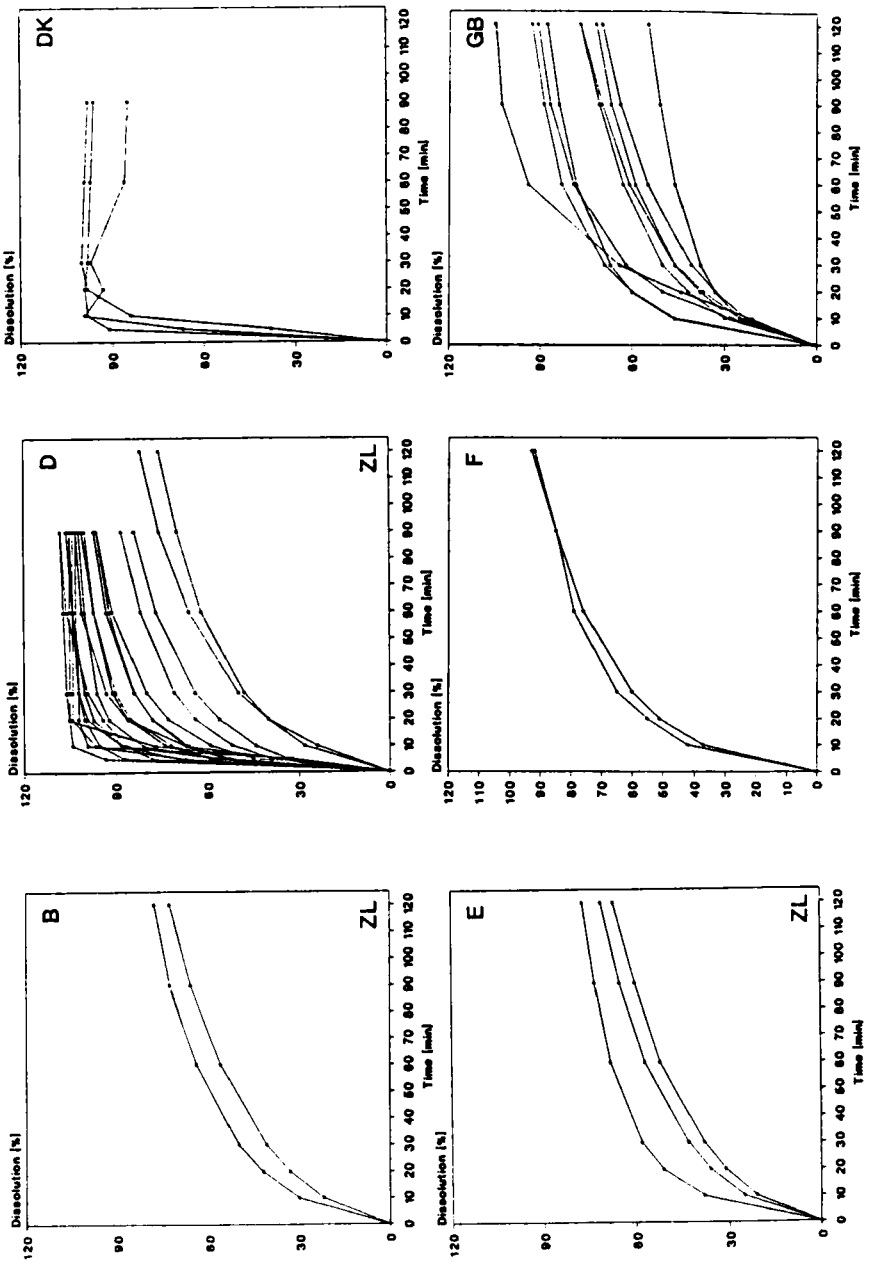

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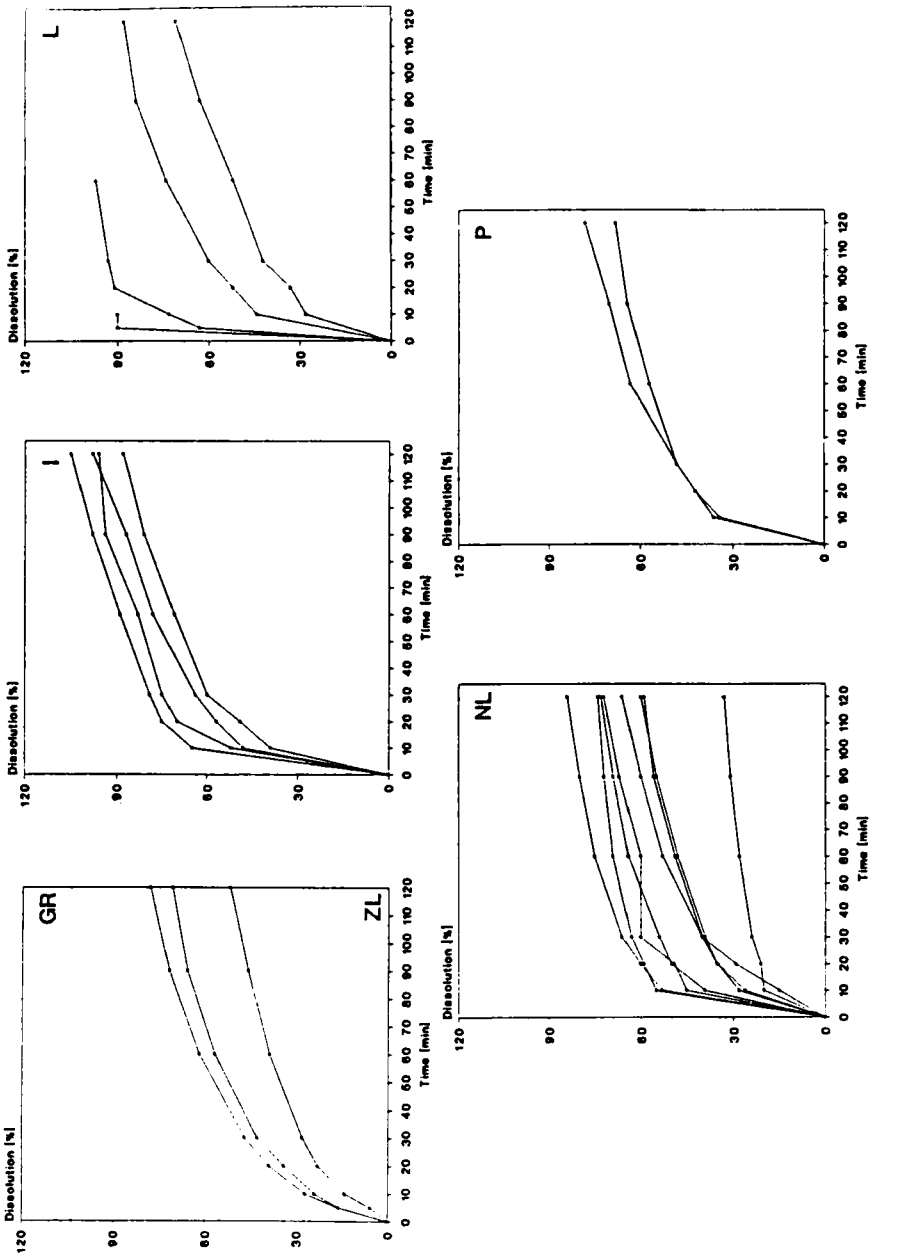

FIGURE 2:
In-vitro Dissolution Profiles of Products marketed in EC Countries

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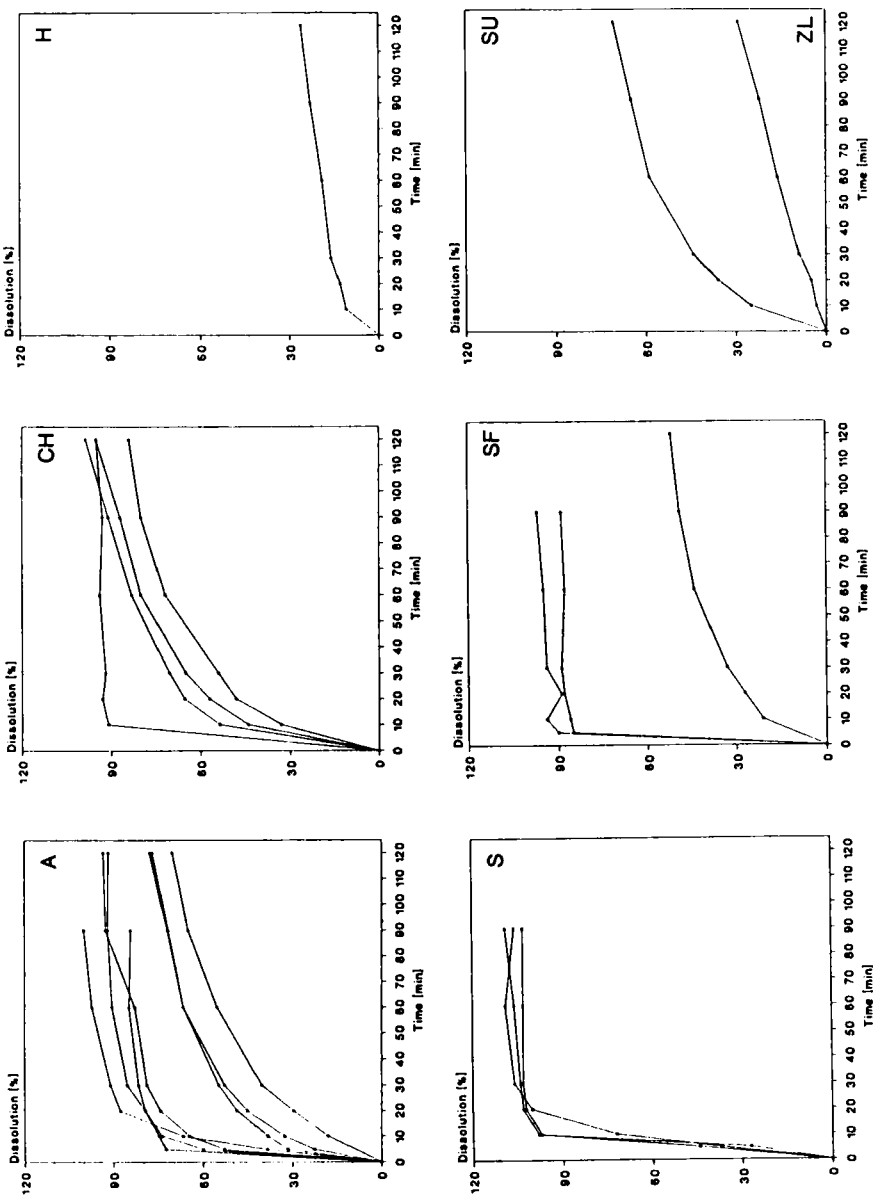

FIGURE 3:
In-vitro Dissolution Profiles of Products marketed in other European Countries

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Results presented in Figs. 2 (EC countries), 3 (other European countries) and 4 (countries from other continents) reveal marked differences in some countries between the various tested products.

In some *EC member states* dissolution properties of marketed glibenclamid tablets are very consistent (e. g. in Belgium, Denmark or France) whereas in others considerable differences in dissolution behaviour were observed (e. g. in Germany, Luxembourg, The Netherlands or United Kingdom) among several products. Similar findings are to be recorded in *other European countries* with rather consistent results in some cases (e. g. in Sweden) and marked differences in others (e. g. in Finland, Austria or Switzerland). In certain *countries from other continents* the quality of marketed glibenclamide products could be qualified as homogenous (e. g. in Thailand or USA), whereas in other cases certain deviations were observed (e. g. in Chile, Japan, Indonesia or Argentina).

While assessing these results it has to be taken into consideration that the marketed products differ in content of the active ingredient (3.5/1.75 or 5.0/2.5 mg). Besides, it is well established in literature [2 - 6, 8] that glibenclamide tablets of 3.5/1.75 mg or 5.0/2.5 mg type exhibit pronounced differences not only in dissolution properties and but also concerning their in-vivo performance (Fig. 5).

Systematic investigations on rate and extent of bioavailability of products exhibiting different dissolution properties have shown that bioavailability clearly depends on dissolution behaviour of Glibenclamide formulations. This applies primarily to the rate of absorption which is strongly associated with the rate of dissolution during the first 10 - 15 minutes. The close correlation of dissolution rate and bioavailability was assessed for several 3.5 mg products on the German market [1 - 5]. These investigations have shown that in particular the plasma concentrations during the first 3 hours after administration are of main importance for the pharmacodynamic effects (reduction of blood glucose levels) observed under treatment.

Thus, products which are markedly differentiated in their in-vitro dissolution properties exhibit also therapeutically relevant differences in bioavailability. As

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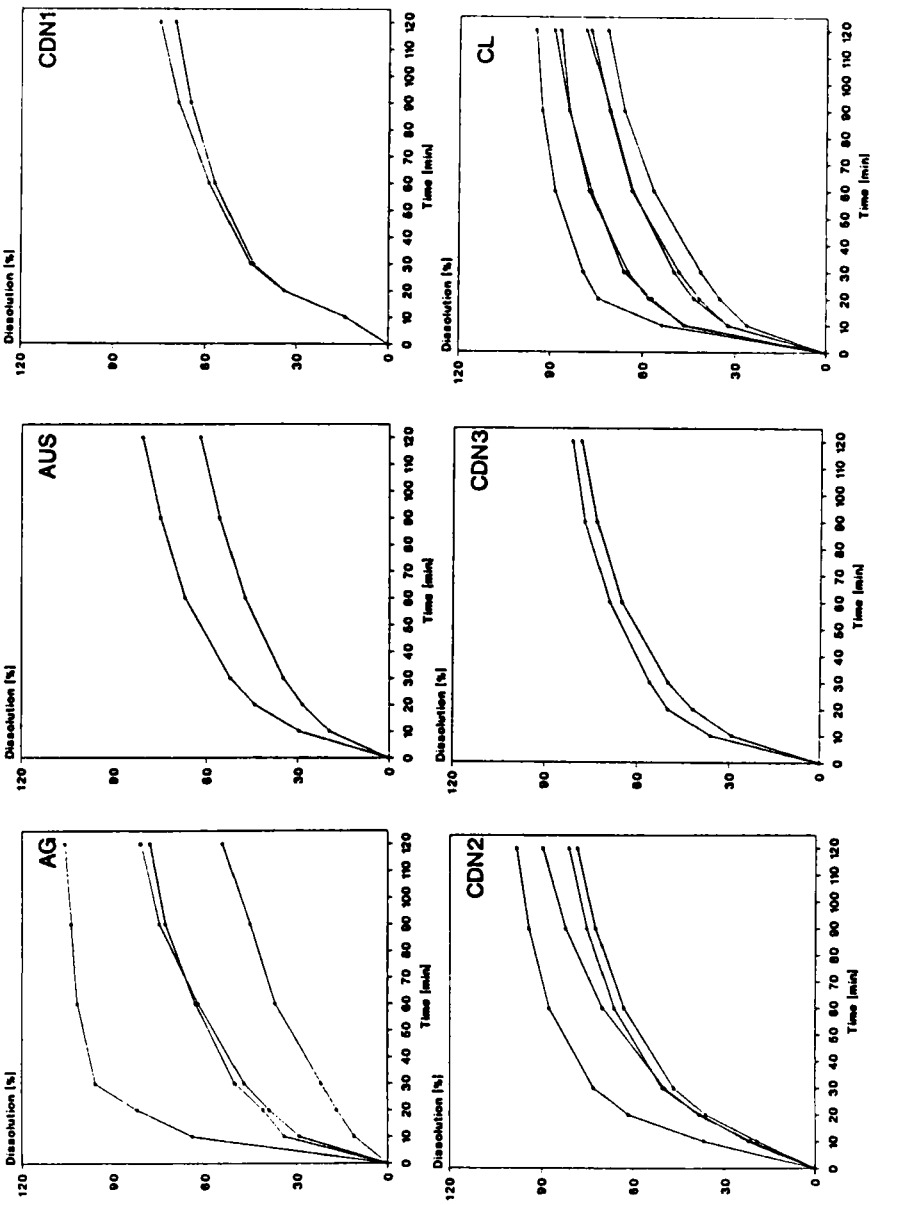

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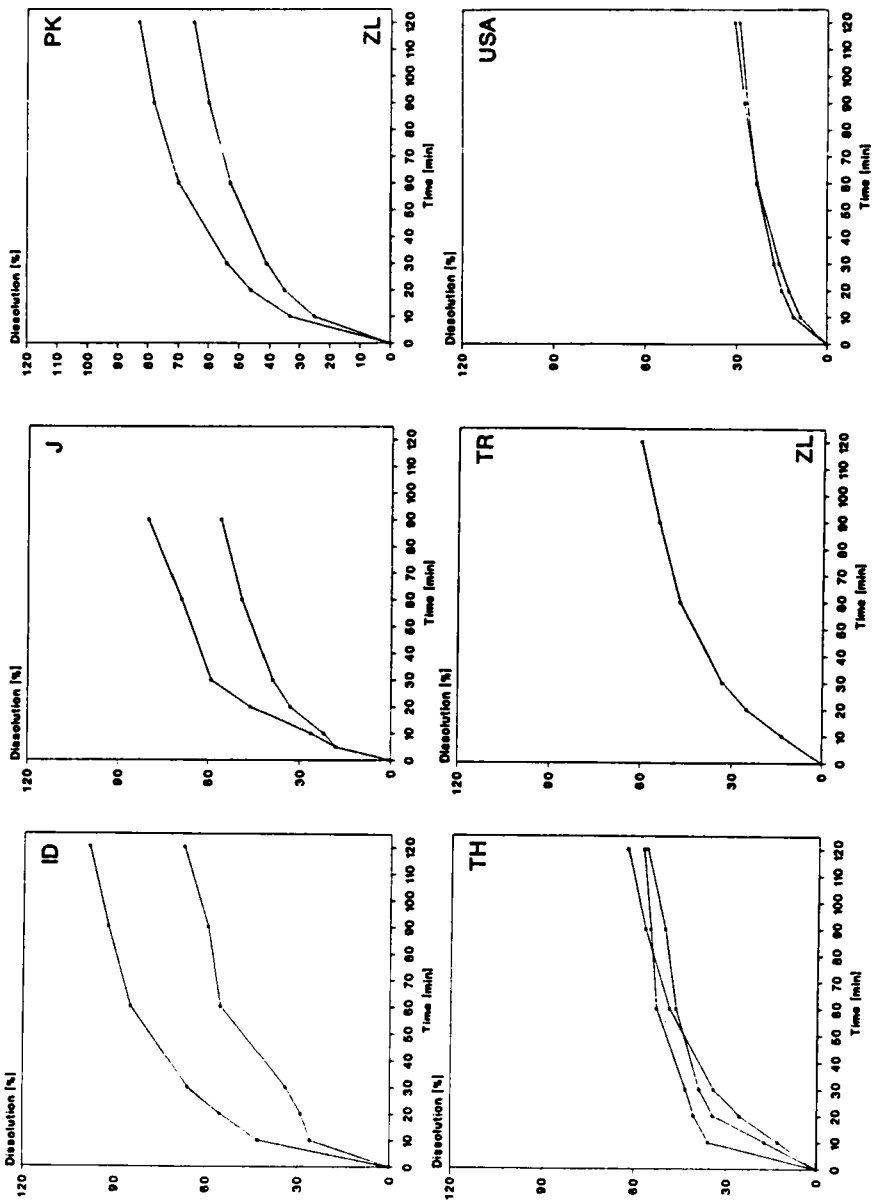

FIGURE 4:
In-vitro Dissolution Profiles of Products marketed in other Countries

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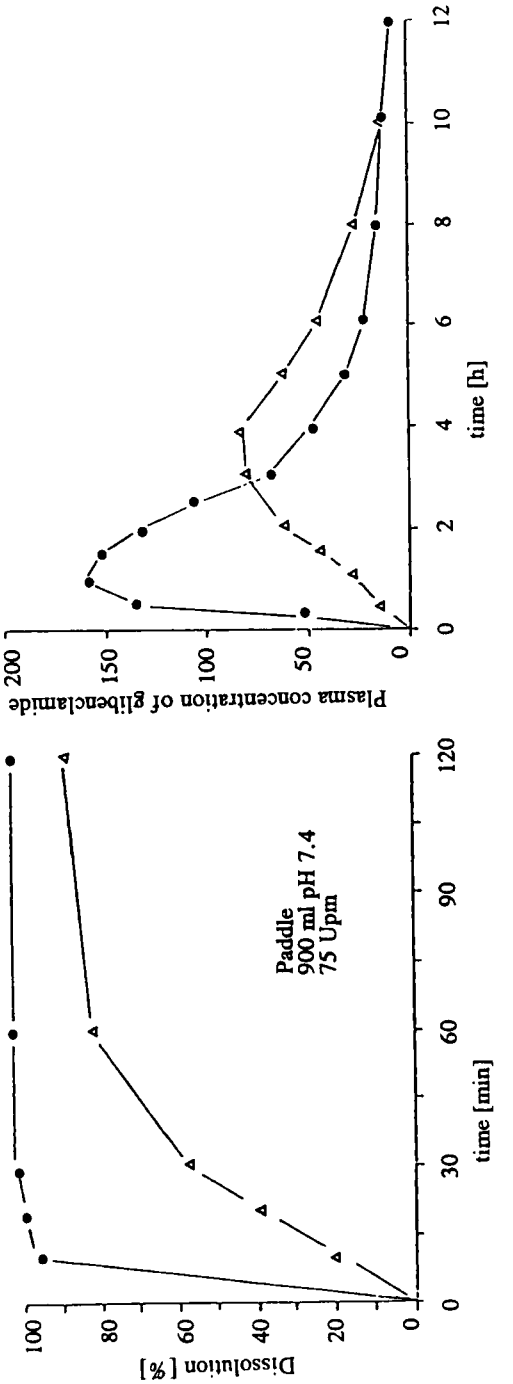

FIGURE 5:
In-vitro Dissolution and corresponding Plasma-Profiles of one 3.5 mg [●] and one 5 mg [▲] Glibenclamide Preparation

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established for 3.5 mg glibenclamide products marketed in Germany, preparations with a dissolution rate of more than 80 % within 10 minutes are obviously bioequivalent with one another but, in contrast, not bioequivalent with formulations which dissolve the active ingredient more slowly.

A further important finding of this multinational study is that also products marketed in different countries can exhibit pronounced deviations in dissolution properties. Thus, for example the two products which are available on the US-market dissolved 30 % of active ingredient within two hours, whereas one 5 mg tablet formulation marketed in Switzerland dissolved the complete dose within 10 minutes under identical experimental conditions. Profiles of all products tested (Figs. 2 - 4) illustrate the pronounced differences in the in-vitro dissolution properties between tablet formulations from various countries.

Although 3.5 mg tablets normally exhibit a higher rate of dissolution compared to a 5 mg tablet, some "overlappings" in this respect were detected. Remarkable examples are the above mentioned 5 mg version in Switzerland which dissolved the active ingredient as fast as "typical" 3.5 mg tablets or on the other hand several 3.5 mg products in Germany with as "retarded" dissolution behaviour as "typical" 5 mg products. In some countries, e. g. U.S.A., CIS or Hungary, 5 mg-tablets are marketed with unusual slow drug release (compared to other countries).

CONCLUSIONS

While most products tested in this multinational postmarket comparative study fulfilled pharmacopeial requirements concerning identity, purity, content (95 - 105 %) and content uniformity (85 - 115 %), there were some that did not comply. For drug content no product was outside the 90 to 110 % range; for content uniformity only one product slightly exceeded the upper 115 % limit.

In contrast, marked differences were recorded concerning dissolution properties. This observation not only applies to products of the respective national markets but also to the comparison of quality standards among products from different countries. From bioavailability studies it is known that such differences in

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dissolution are also clinically relevant (8). In this respect it is worth mentioning that some cases of therapeutic failures were reported in Germany (9 - 11) which can be attributed to slow dissolution profiles.

It can be concluded that these findings are equally relevant for products marketed in other countries, also for 5.0/2.5 mg versions. For very-slow releasing 5 mg dosage forms low bioavailabilities (partial AUC in the first three hours) and, consequently, poor pharmacodynamic effects (reduction of blood glucose levels) have to be expected. On the other hand the immediate-release 5 mg preparation from Switzerland will presumably cause excessive clinical effects when substituted for the innovator's formulations. However, this assumption has to be confirmed by further in-vivo studies.

Pharmacists as well as physicians will need actual informations concerning the biopharmaceutical quality of products marketed in their countries to safeguard optimum and efficient drug therapy with glibenclamide tablets. Preparations which dissolve more than 80 % of the active ingredient within 10 - 15 minutes are anticipated to be interchangeable with one another, but non-interchangeable with formulations of a lower dissolution rate.

Multinational marketing, especially re- or parallel imports from other countries, should be essentially linked with full information on biopharmaceutical performance of the products to pharmacists and physicians.

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