Dissolution Testing as a Prognostic Tool for Oral Drug Absorption: Dissolution Behavior of Glibenclamide

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Purpose. The dissolution behavior of two commercially available glibenclamide formulations was tested in various media. The aim of the study was to investigate whether the use of biorelevant dissolution media (BDM) would be advantageous over the use of standard media for predicting the *in vivo* performance of the two formulations.

Methods. The dissolution tests were performed using USP 23 apparatus 2. Conventional buffers and USP media were compared with two BDM containing different amounts of lecithin and sodium taurocholate.

Results. The dissolution of two drug powders was highly dependent on wetting, particle size, pH, and the composition of the medium used. In addition, the dissolution behavior of the two glibenclamide formulations showed differences in all media tested. The dissolution results of the two formulations were compared with those from an *in vivo* bioequivalence study undertaken by the central quality control laboratory of the German pharmacists (ZL). The bioequivalence criterion set by the ZL requires more than 80% drug release within 10 minutes. Results in FaSSIF, one of the BDMs, met the ZL criterion and this medium was also able to discriminate between the two formulations. This was not the case for the other media tested.

Conclusions. The study indicates that BDM are better able to discriminate between glibenclamide formulations than standard dissolution media.

KEY WORDS: dissolution test; glibenclamide; bioequivalence.

INTRODUCTION

Dissolution tests are a standard method used to ensure the batch to batch conformity of oral dosage forms. In research and development, dissolution tests are often used to assist in the formulation development of IR and MR dosage forms. Today most pharmacopeias describe four different dissolution test apparatuses: basket, paddle, reciprocating cylinder and flow-through cell. The most often recommended methods are the basket and the paddle because of their precise and simple set-up and handling (1). Even though these closed systems normally simulate only one GI environment within a given run, they are suitable for characterizing the drug release from many formulations.

In addition to the apparatus and its influence on the dissolution of a substance, the choice of a suitable dissolution medium is a critical parameter. National pharmacopeias describe various test media such as SIF or SGF to cover the physiological pH range between 1.2 and 7.5 (2). But for many drugs which are poorly soluble over this pH range these media are not very useful. In such cases surfactants such as sodium lauryl sulfate (3), emulsions (4), higher pH values, or even organic solvents are added to the media to improve the solubility of the drug (5). The use of cosolvents can be problematic particularly for MR dosage forms, since they can interact with the release controlling mechanism of the formulation and therefore regulatory agencies tend to discourage their use (1). An alternative way to investigate the quality of a formulation and to improve the *in vitro/in vivo* correlation (IVIVC) is to use non-pharmacopeial dissolution media or conditions (6,7). However, the choice of the best medium, i.e. one that can discriminate between critical manufacturing variables, is crucial in this case. New biorelevant dissolution media (BDM) containing lecithin and sodium taurocholate in physiologically amounts (8) have been proposed to obtain a better understanding of the dissolution process *in vivo* and to predict oral drug absorption (9,10).

Glibenclamide is an oral hypoglycemic agent with poor aqueous solubility. It was chosen as a test drug substance on the basis of its low aqueous solubility. As a weak acid with a pKa of 5.3 (11) its solubility strongly depends on the pH of the test medium. The dissolution behavior of glibenclamide from two products, one of which is still commercially available on the German market, as well as the dissolution of pure powder with different particle sizes was studied. It was expected that the drug substance properties (particle size) as well as the composition of the medium would highly influence the dissolution behavior of glibenclamide.

It is recommended that glibenclamide tablets should be taken in the fasted state (12). For this reason we tested the formulations mostly under simulated fasted state conditions. In some cases we also tested the dissolution behavior in fed state simulating intestinal fluid (FeSSIF), to gain a better understanding of the interaction between pH and bile effects on the dissolution of the drug substance.

MATERIALS AND METHODS

Materials

Sodium taurocholate 98 % pure, Lot # 15H5001 was purchased from Sigma-Aldrich Chemie GmbH (Deisenhofen, Germany). Egg-phosphatidylcholine, Lipoid E PC 99.1% pure, lot # Egg-phosphatidylcholine, Lipoid E PC 99.1% pure lot #12091-1, was a gift from Lipoid GmbH (Ludwigshafen, Germany).

Potassium dihydrogen phosphate, potassium chloride, sodium chloride, pepsin, and hydrochloric acid (all analytical grade) were purchased from E. Merck (Darmstadt, Germany). Glibenclamide powder Lot # N 392 (Hoechst AG) and glibenclamide powder microfine Lot # N 326 (Hoechst AG) was a gift from Hoechst AG (Frankfurt, Germany).

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Dissolution

An Erweka Type DT 6 dissolution tester (Erweka, Heusenstamm/Germany) was used for all dissolution studies. The apparatus was calibrated according to the USP 23. The dissolution in various test media was tested using the paddle method (method 2 USP 23), employing 500 or 900 ml of dissolution medium at a temperature of 37 ± 0.5°C, and an agitation rate of 75 rpm.

Composition of Dissolution Media

Simulated Intestinal Fluid: SIF_{sp}, which has a pH of 7.5, was composed as SIF, USP 23, without pancreatin (2).

Fasted State Simulating Intestinal Fluid: FaSSIF contains 3 mM sodium taurocholate and 0.75 mM lecithin and has a pH of 6.5 and an ionic strength of 0.15 (13). $FaSSIF_{slt}$ (sine lecithin, taurocholate) was composed as FaSSIF, but without lecithin and sodium taurocholate.

Fed State Simulating Intestinal Fluid: FeSSIF contains 15 mM sodium taurocholate and 3.75 mM lecithin and has a pH of 5.0 and an ionic strength of 0.3 (13). $FeSSIF_{slt}$ (sine lecithin, taurocholate) was composed as FeSSIF, but without lecithin and sodium taurocholate.

Simulated Gastric Fluid: SGF was prepared according to the USP 23, without pepsin (2).

Buffer pH 6.0: was a 20 mM potassium phosphate buffer of pH 6.0.

Protocol for Glibenclamide 3.5 mg Tablets and Glibenclamide Powder

Dissolution tests were performed on Euglucon N® 3.5 mg Tablets hereafter designated as ,,reference product,, (Lot # 01N620, Boehringer Mannheim/Hoechst, Germany), on Glukovital® 3.5 mg Tablet, hereafter designated as ,,test product,, (Lot #09601, Dr. August Wolff Arzneimittel, Bielefeld, Germany), on glibenclamide powder (Lot # N392, Hoechst AG, Frankfurt, Germany), and on glibenclamide microfine powder (Lot #N326, Hoechst AG, Frankfurt, Germany).

Sampling Procedure

Samples were removed using a 5 ml Fortuna Optima syringe fitted with custom made steel tubing equipped with a filter to facilitate representative sampling. 15 seconds before the sample was taken, the steel tube was lowered into the dissolution medium. The drawn sample volume was replaced with the same volume of blank dissolution medium from a separate vessel, also held at a temperature of 37 ± 0.5°C. The sample was then filtered through a 0.45 μm (Schleicher & Schuell FP 030/20) cellulose acetate filter, discarding the first 2–3 ml. Samples were kept in 25 × 10 mm screw cap glass test tubes until analysis. Filter and steel tubing were checked for adsorption, but no significant loss of drug was observed.

HPLC Analysis

A Merck Hitachi HPLC-system composed of an L 7200 Auto sampler, a pump L7100 and an UV Detector L4250 (Merck Hitachi, Darmstadt, Germany) was used for sample analysis. 30 μl of the dissolution samples were directly injected on the column without further preparation. As an analytical column LiChoCART 125-4 LiChospher 60 Rp-select B (5 μm, Merck, Darmstadt, Germany) with a guard column was used. The mobile phase was a mixture of acetonitrile and sodium dihydrogen phosphate buffer (25 mM, pH 4.5) in a ratio of 45:55. The flow rate was 1 ml/min and the wavelength was 230 nm. The retention time of glibenclamide (8 minutes) separated the drug adequately from other media components. No drug instability was detected in any media within the assay time. A six point standard curve was constructed for each dissolution media and linearity was confirmed throughout a detection range of 0.1% to 150% of the expected drug content. The data were stored in an a Shimadzu C-R5A integrator (Shimadzu, Kyoto, Japan) and were transferred to Excel (Microsoft, CO) for data analysis.

Surface Tension, pH Measurements, and Particle Size

Surface tension of the various dissolution media was measured at 20°C by the ring method using a tensiometer (Lauda TE 1, Lauda, Germany). The change in pH was measured 30 minutes after adding a tablet to 10 ml of water. The particle size was determined using a light microscope (Carl Zeiss, Jena) equipped with a scale. The quality control laboratory at Hoechst AG determined the surface area of both powders (14).

Dissolution Test Conditions and IVIVC-Requirements for Glibenclamide Products

Studies carried out by the central quality control laboratory of the German pharmacists (ZL) used 900 ml of a buffer with a pH of 7.4, and USP apparatus 2 with an agitation rate of 75 rpm. A relationship was found between the extent of dissolution in the first 10 minutes and the glucose levels in the first 3 hours (15). According to these findings, a new product should release not less than 80% of the drug within 10 minutes *in vitro* in order to achieve bioequivalence to the pioneer product (15).

In Vitro/*In Vivo* Correlation

The percent absorbed for both formulations was calculated from the bioequivalence study undertaken at the ZL (15) using the software Kinetica™ (InnaPhase, 77420 Champs sur Marne, France). The data were calculated using the Loo-Riegelman two compartment model. Because no i.v. data were available, the oral data after C_{max} were used to calculate pharmacokinetic parameters. The *in vivo* data for the time points at 30, 60, 90, and 120 min. were then correlated with the *in vitro* dissolution data at 5, 10, 15, and 30 min.

Computer Simulation

A useful tool to predict the plasma concentrations of a drug is the Biopharmaceutics Classification System (BCS) (16,17). Key parameters are permeability and the concentration at the intestinal membrane, which is generated by drug dissolution and is therefore dependent on drug solubility. The calculations in Gastro Plus™ are based on these principles and the model is known as the advanced compartmental absorption and transit model (ACAT) (18). A closer description of the software can be found on the company's home page: http://www.simulations-plus.com.

The computer simulation was performed using Gastro Plus™ Version 1.05 (Simulations Plus, Lancaster, CA). The

input data for the chemical properties were taken from literature (11,19) or were calculated using suitable software. The log P was calculated by free software available on the Internet (http://esc.syrres.com), the diffusion coefficient was calculated according to the Hayduk-Laudi-Correlation (20) and the P_{eff} was estimated by the simulation software. The particle radius was set at 50 μ, corresponding to the microscopic analysis of the powder. The "solubility" for each formulation was based on the maximum amounts dissolved in FaSSIF in the dissolution tests.

The pharmacokinetic parameters, clearance, volume of distribution, K_{12}, K_{21} used in Gastro Plus™ for the simulation were calculated using Kinetica™. Model fits to the experimental *in vivo* data confirmed that the pharmacokinetics could be best described by a two-compartment model (21), which was then used for the simulation in Gastro Plus™.

Data Analysis and Statistics

Dissolution data is presented as mean ± sd (n = 3). Linear regression was used to test for correlation between the dissolution behavior in different media and the *in vivo* data (SigmaPlot 5.0, SPSS, Chicago). The goodness of fit of the simulated to the observed curve was assessed graphically by plotting the observed data versus the simulated data using SigmaPlot software (SigmaPlot 5.0, SPSS, Chicago). Linear regression was applied to the data to determine whether they fell within the predetermined confidence interval of 99%.

RESULTS

Dissolution Results with Glibenclamide Powder

The microscopic analysis of the two powders showed a significant difference in the particle size and size distribution. While 99% of the microfine powder had a particle size of approximately 50 μm, the "normal" powder showed particle sizes between 50 μm and 350 μm. According to the manufacturer, the surface area of the microfine powder is 4.6 times higher than the normal powder (14). In pH 5 buffer ($FeSSIF_{slt}$) no dissolution was detected within 60 minutes for either powder. Addition of bile components improved dissolution, but due to the unfavorable pH, only 2–4% dissolved within one hour. At pH 6.5, dissolution was still poor in absence of bile components, but in FaSSIF 17% of micronized powder and 3–6% of normal powder dissolved within an hour. At pH 7.5 (SIF_{sp}) differences in dissolution with particle size were also observed. The more favorable pH failed to compensate for the lack of bile components, though, with the result that less than 10% of either powder dissolved with in one hour.

Dissolution of the Two Glibenclamide Formulations: Effect of Volume

In a preliminary series of experiments using the two formulations, the influence of the media volume on the dissolution rate was tested. Both formulations were tested in 500 and 900 ml of SIF_{sp} by the paddle method. The volume appeared to have no effect on the release rate of the test formulation, while the release from the reference formulation was decreased at the lower volume, see Table 2.

Dissolution of the Reference Formulation in 500 ml of Different Media

In pH 7.5 buffer (SIF_{sp}) over 90% of the drug content of the reference product dissolved within 10 minutes. This formulation therefore met the ZL criterion of 80% release within 10 minutes. After 30 minutes approximately 100% of the drug content was dissolved (Fig. 1). In pH 6.5 buffer ($FaSSIF_{slt}$) only 34% of the drug content dissolved in one hour. This concentration appears to correspond to saturation with glibenclamide in 500 ml at this pH and for this formulation. In a pH 6.0 buffer only half this amount (18%) was dissolved after one hour. In pH 5.0 buffer ($FeSSIF_{slt}$) only 1.4% of the drug could be dissolved in 500 ml. In dissolution media containing lecithin and sodium taurocholate the dissolution rate was improved. In FaSSIF (pH 6.5) up to 87 % of the drug content was dissolved, while in FeSSIF (pH 5.0) 18% of the glibenclamide was dissolved, see Fig. 1.

Dissolution of the Test Formulation in 500 ml of Different Media

The release of glibenclamide from the test formulation in SIF_{sp} was not as fast as for the reference product. The test

Table 1. Dissolution Test Results for Two Types of Glibenclamide Powder in 500 ml of Dissolution Medium with Apparatus 2 (Paddle) at a Speed of 75 rpm, Expressed as % Release from Two Experiments

Medium & pH	SIF 7.5		FaSSIF 6.5		$FaSSIF_{slt}$ 6.5		FeSSIF 5.0		$FeSSIF_{slt}$ 5.0	
time	normal	microfine	normal	microfine	normal	microfine	normal	microfine	normal	microfine
5	<0.1	<0.1	0.88	0.7	NM[a]	NM[a]	<0.1	<0.1	<0.1	<0.1
	<0.1	<0.1	0.1	1.6			<0.1	<0.1	<0.1	<0.1
10	0.3	1.2	1.1	2.1	<0.1	<0.1	<0.1	<0.1	<0.1	<0.1
	0.1	0.2	0.4	4.2	<0.1	<0.1	0.4	0.4	<0.1	<0.1
20	0.9	2.7	NM[a]	NM[a]	NM[a]	NM[a]	NM[a]	NM[a]	NM[a]	NM[a]
	0.2	1.6								
30	NM[a]	NM[a]	3.6	9.0	<0.1	<0.1	1.4	0.2	<0.1	<0.1
			1.7	12.5	<0.1	<0.1	2.0	2.1	<0.1	<0.1
60	4.2	9.3	6.3	17.3	0.4	0.5	2.3	2.1	<0.1	<0.1
	1.3	7.3	3.2	17.0	0.6	0.2	2.9	4.3	<0.1	<0.1

[a] NM = not measured.

Table 2. Dissolution Test Results for the Reference and the Test Formulations in 900 and 500 ml of SIF_{sp} with Apparatus 2 (Paddle) at a Speed of 75 rpm, Expressed as Mean % Release ± Standard Deviation

	Reference formulation		Test formulation	
time	500 ml	900 ml	500 ml	900 ml
5	70 ± 0.4	83 ± 5	35 ± 3	32 ± 3
10	93 ± 3	100 ± 0.4	75 ± 0.5	71 ± 4
15	98 ± 2	100 ± 1	92 ± 2	90 ± 3
30	100 ± 2	100 ± 1	107 ± 1	105 ± 2
60	100 ± 1	100 ± 2	115 ± 1	113 ± 1

formulation failed to meet the ZL criterion of 80% release within 10 minutes (15). In FaSSIF containing lecithin and sodium taurocholate up to 40% of the drug dissolved in one hour, which is less than the half the amount from the reference product dissolved in the same medium. In $FaSSIF_{slt}$, however, approximately 31% of the drug dissolved in one hour, nearly the same as determined for the reference product in the same medium. In $FeSSIF_{slt}$ no drug could be detected after one hour of testing, see Fig. 2.

Surface Tension and pH Measurements

Surface tension of the different media was determined. The value for water was found to be 72 dyne/cm while FaSSIF showed a much lower value of 49 dyne/cm. The reference formulation lowered the surface tension of 500 ml SIF from 65 to 49 dyne/cm. The test formulation changed the surface tension of 500 ml SIF from 65 to 62 dyne/cm. This indicates that the reference product contains more/more efficient surfactants than the test product. These may improve wetting of glibenclamide and thus have an impact on its dissolution rate (4). Both formulations increased the pH of 10 ml of water from 6.18 to 6.76 for the reference and to 6.97 for the test formulation. This slight increase in the pH indicates that little or no pH increasing excipients were used in either formulation to encourage the dissolution.

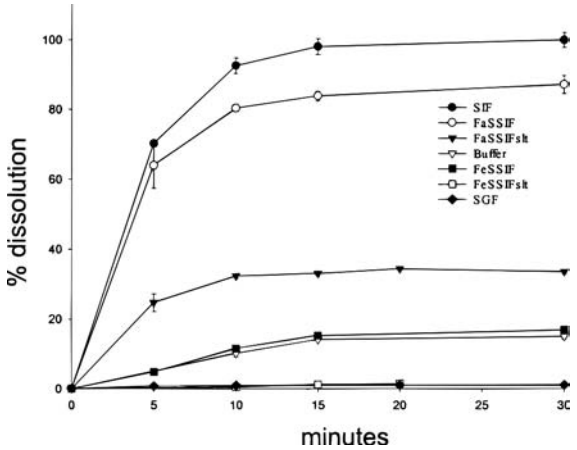

Fig. 1. Dissolution of the reference formulation (± sd) in various test media using the paddle method (method 2 USP 23), employing 500 ml of dissolution medium at a temperature of 37 ± 0.5°C, and an agitation rate of 75 rpm.

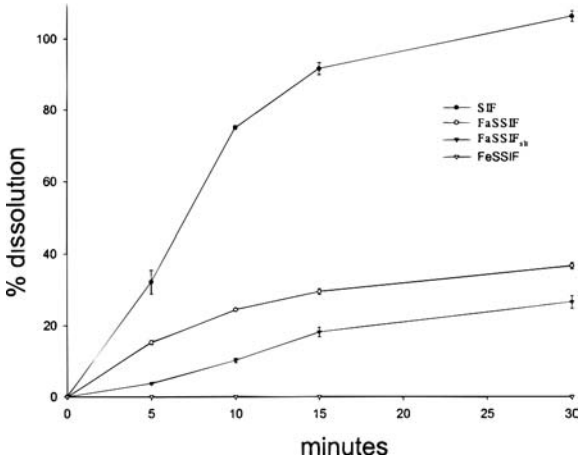

Fig. 2. Dissolution of the test formulation (± sd) in various test media using the paddle method (method 2 USP 23), employing 500 ml of dissolution medium at a temperature of 37 ± 0.5°C, and an agitation rate of 75 rpm.

IVIVC

The results of the *in vitro/in vivo* correlation are shown in Fig. 3. The graph shows that if FaSSIF was used as the dissolution medium both formulations showed an essentially linear relationship. The slopes of the regression lines using FaSSIF are similar at 3.27 for the test and 3.33 for the reference product. In contrast, the correlation curves in SIF are not linear and have obviously different curvatures (slopes of the best linear fits are 0.9 and 1.88 respectively).

Software Analysis of the *In Vivo* Data and Simulations

A comparison of the different pharmacokinetic parameters obtained by the Gastro Plus™ simulation, pharmacokinetic fitting (with Kinetica™) and those reported by the manufacturer of the test formulation is given in Table 3. While the data provided by the manufacturer overestimate the actual (taken from the raw data) C_{max} values for the two formulations, both Gastro Plus™ and Kinetica™ underestimated C_{max}. The observed mean plasma levels from the bioequivalence study

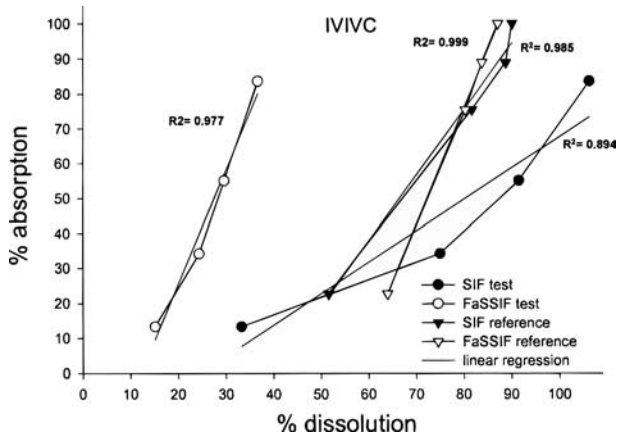

Fig. 3. *In vitro/in vivo* relationship of the two commercially available formulations in SIF_{sp} and FaSSIF.

Table 3. Comparison of Pharmacokinetic Parameters Provided by the Manufacturer, Calculated Using Simulation Software (Gastro Plus™), and Fitted to a Two Compartment Model Using Kinetica™ [b]

	Manufacturer		Gastro Plus™		Kinetica™	
	Reference[a,c]	Test[a,c]	Reference	Test	Reference	Test
C_{max} (ng/ml)	334	238	272	207	293	179
t_{max} (hours)	1.7	3.0	1.65	2.13	1.40	2.30
$t_{1/2}$ (hours)	1.74	3.57	1.34	2.60	1.34	2.60
AUC_{0-24} (ng/ml*h)	1387	1458	1190	1140	1463	1691

[a] Data for Euglucon N (Boehringer Mannheim/Hoechst).
[b] Data for Glukovital (Wolff).
[c] Data supplied by Wolff.

are shown in Fig. 4. The t_{max} values in the three parameter sets also exhibit differences (see Table 3). The lower AUC obtained with Gastro Plus™ seems to be due to the lower C_{max} and t_{max} values, see Fig. 3. A close simulation of both observed plasma curves was only successful when the dissolution results of the experiments in FaSSIF were used in Gastro Plus™ for each formulation separately. The goodness of fit for the test formulation showed that, except for the 1 and 1.5 hour data, all data pairs (simulated vs. observed) were within a 99% confidence interval, and the regression coefficient was 0.89. For the reference formulation all data points, except for 3 hours, were within a 99% confidence interval with a regression coefficient of 0.97.

DISCUSSION

Two different glibenclamide powders are commercially available from Hoechst AG. The dissolution results in different media show that the rate and extent of drug dissolution highly depends on the wetting characteristics of the medium used as well as on the particle size of the powder. The smaller particles with the higher surface area (microfine powder) dissolved faster compared to the bigger particles of the non-micronized powder. This could result in incomplete absorption from the coarser powder, depending on the particle size, as the transit time may be too short for complete dissolution of the drug. In the case where particle size is large, glibenclamide can be considered as a dissolution-limited drug (Dissolution Number < 1) (4,22).

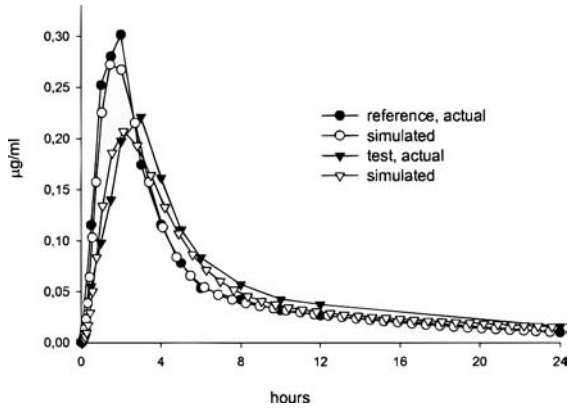

Fig. 4. Observed and simulated mean plasma curves of a single dose of the reference and the test formulation. Data for the observed values are taken from (15).

The Dissolution Number (Dn), which is the ratio between transit time and dissolution time, can be increased by reducing the particle size (17). Another way to improve oral absorption is to decrease the Dose Number, which is defined as the ratio of dose concentration to drug solubility (17). In the case of glibenclamide, physiological concentrations of solubilizers like lecithin and sodium taurocholate can improve the solubility substantially (compare results for both powders in FaSSIF and SIF_{sp}). Furthermore, the interaction of the lecithin/taurocholate micelles with excipients can significantly improve the solubility of the drug, as shown for both oral formulations in FaSSIF. The small change in pH of an aliquot of water due to addition of the dosage form indicates that the increase in the solubility was due to surface-active excipients in the formulations and not to addition of pH increasing excipients.

Although, most formulations in Germany contain a dose of 3.5 mg glibenclamide, there are also products marketed in Europe containing 5 mg drug (23). It has been shown that dosage forms containing 3.5 mg have the same therapeutic effect as formulations with 5 mg (24). This unusual result can be explained by the slower and presumably incomplete absorption of the larger drug particles used in the 5 mg formulations.

The biopharmaceutical quality of different glibenclamide products was investigated by Blume et al. (23). The results showed high variability in the dissolution behavior, even for the same brand name product manufactured in different countries. Systematic investigations by the ZL of the rate and extent of bioavailability of glibenclamide products on the German market containing 3.5 mg drug and exhibiting different dissolution properties have shown that bioavailability can be clearly correlated with the dissolution behavior of glibenclamide formulations (15). From the bioavailability studies it is known that such differences in dissolution are also clinically relevant (23). Investigations have shown, in particular, that the plasma concentrations during the first three hours after administration are of major importance for the pharmacodynamic effect (24). The rate of absorption in the first three hours is, in turn, strongly correlated with the rate of dissolution during the first fifteen minutes in SIF_{sp}. The *in vivo* data published by ZL show the same tendency as our *in vitro* results for the reference product and the test formulation.

A close linear relationship between percent dissolved within 30 minutes and percent absorbed within 2 hours was found in our investigation, see Fig. 3. The improved linearity

using FaSSIF as a dissolution medium indicates that this medium reflects the *in vivo* dissolution conditions more closely than the compendial SIF. Furthermore, the regression lines for both formulations are nearly parallel if FaSSIF is used. This observation suggests that FaSSIF is better able to discriminate between formulations than SIF. A better simulation of the *in vivo* conditions is the key to a more precise prediction of the oral absorption of a drug. It is clear from our results that a correlation can be developed for BCS case 2 drug products using BDM, and that more than one dissolution time point is needed to characterize release from the dosage form completely. This is consistent with the FDA guideline for IR products i.e. "for slowly dissolving or poorly water soluble drugs (BCS case 2), a two point dissolution specification, one at 15 minutes to include a dissolution range (dissolution window) and the other at a later point (30, 45 60 minutes) to ensure 85 % dissolution is recommended to characterize the quality of the product" (1). According to the present data, an *in vitro* difference in the dissolution behavior even within the first 10 minutes can predict a different bioavailability. The difference in the *in vitro* and *in vivo* time scales suggest that further adjustment of the *in vitro* dissolution parameters may be needed to better simulate the *in vivo* conditions.

CONCLUSIONS

Our results clearly show that the dissolution of glibenclamide products is influenced by several parameters, the most important of which are the pH of the media and the presence of dissolution enhancers in the formulation. Media containing lecithin and sodium taurocholate increase the dissolution of glibenclamide, but the degree to which this occurs is dependent on the level of surface-active excipients in the formulation. The higher solubility of the reference product in FaSSIF may result from the presence of emulsifiers or other dissolution enhancers in the formulation, as indicated by the surface tension results. Of the various media tested, FaSSIF seems to be the most suitable medium for showing differences between formulations over a time frame that is consistent with physiological and pharmacological events. Strong correlations were observed between dissolution in FaSSIF and absorption for both glibenclamide products. The dissolution results in FaSSIF were also suitable for predicting the oral absorption of the tested formulation using the ACAT model. Correlations with SIF failed to achieve linearity and varied widely with product, indicating a clear advantage of BDM over simple buffer systems for IVIVC of glibenclamide products.

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