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Use of Isosorbide Dinitrate Saliva Concentrations for Biopharmaceutical Investigations

H. LAUFEN ˣ, M. SCHMID, and M. LEITOLD

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Abstract □ The concentration of isosorbide dinitrate in paired samples of plasma and mixed saliva was monitored for up to 24 hr after oral administration of 60 mg of sustained-release isosorbide dinitrate to eight healthy volunteers. Measured isosorbide dinitrate plasma concentrations were mainly in the range of 0.1–10 ng/ml. Isosorbide dinitrate was excreted into saliva resulting in a mean (±*SD*) saliva–plasma concentration ratio of 0.68 ± 0.37. A significant correlation between concentrations of isosorbide dinitrate in saliva and plasma was found ($p < 0.01$). The sustained-release properties of the administered formulation were confirmed from the concentrations of isosorbide dinitrate found in both saliva and plasma. Saliva–plasma ratios were independent of the absolute concentrations of isosorbide dinitrate but showed a slight tendency to decrease with time. The principal factor relating saliva and plasma isosorbide dinitrate concentrations appeared to be the degree of plasma protein binding of the drug.

Keyphrases □ Isosorbide dinitrate—saliva–plasma ratios following oral administration of a sustained-release preparation □ Sustained-release formulations—saliva–plasma ratios of isosorbide dinitrate following oral administration □ Excretion, salivary—use of isosorbide dinitrate saliva concentrations for biopharmaceutical investigations □ Pharmacokinetics—use of isosorbide dinitrate saliva concentrations for biopharmaceutical investigations

In recent years many investigations have been made on the salivary excretion of drugs in humans. For a number of drugs, it has been demonstrated that the measurement of their concentrations in saliva can be a convenient substitute for plasma analyses, both in monitoring therapeutic drug concentrations and in pharmacokinetic and biopharmaceutical studies. The advantage offered by the measurement of drug concentrations in saliva as well as the limitations of this procedure have been the subject of recent reviews (1–8).

Whether salivary concentration measurements are of value in monitoring pharmacokinetic properties of drugs or not depends on how closely saliva and plasma levels are related. Variations in the saliva–plasma ratio are produced by a number of factors, including variation of the pH of plasma and saliva, the extent of the drug's plasma protein binding, salivary flow rate, active secretion processes, buccal reabsorption, delayed appearance of the drug in saliva, and the technique of saliva sampling (9).

Isosorbide dinitrate is used in the treatment of coronary disease. The plasma pharmacokinetics of this drug are characterized by its rapid excretion (10). This is a disadvantage in long-term therapy with isosorbide dinitrate, and a sustained-release oral formulation of the drug has been used in an attempt to overcome this problem (11–17). During the development of a sustained-release preparation of isosorbide dinitrate, the usefulness of salivary concentration monitoring by multiple paired measurement of isosorbide dinitrate in saliva and plasma was tested.

The present report describes the saliva–plasma ratios of isosorbide dinitrate in eight healthy humans following oral administration of 60 mg of a sustained-release preparation.

EXPERIMENTAL

Eight healthy, fasted, volunteers (3 females and 5 males; 18–38 year; 42–75 kg) were each given one capsule of a slow-release formulation of isosorbide dinitrate[1] (60 mg) with 100 ml of water. Three hours after drug ingestion, a normal breakfast was taken. Blood samples were collected by venipuncture at 0, 0.25, 0.5, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 15, and 24 hr after drug administration. At each time the volunteers expectorated 1 ml of mixed saliva into a glass vial. When necessary, to enhance the spontaneous saliva flow, a small crystal of citric acid was applied to the volunteer's tongue. Saliva and plasma (separated from whole blood by centrifugation) were stored at −30° until analysis. Concentrations of isosorbide dinitrate in plasma and saliva were determined by an identical GC procedure with an internal standard (18). The lower limit of isosorbide dinitrate detection was 0.05 ng/ml. All analyses were performed in duplicate.

Statistical calculations on the concentration data obtained were performed with a desk-top computer[2]. The correlation of saliva and plasma levels was determined by linear regression. The coefficient of regression was tested for significant difference from zero, the 95% confidence limits of the coefficient of regression were calculated, and an analysis of variance of the regression was performed (19). Using the same procedures, possible correlations of the saliva–plasma ratio with the absolute plasma concentrations of isosorbide dinitrate as well as with sampling time were tested. The areas under the saliva and plasma level curves were calculated using the trapezoidal rule. An approximate estimation of the apparent

[1] Iso Mack Retard 60 mg, batch No. Ph 2009.
[2] Hewlett-Packard 9815.

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Table 1—Individual and Mean Saliva–Plasma Ratios of Isosorbide Dinitrate Concentrations [a]

Time, hr	Volunteer 1	2	3	4	5	6	7	8	Mean	*SD*
0.25	1.73	0.44	0.77	—	2.25	—	0.00	0.50	0.95	0.86
0.5	1.67	0.66	1.13	0.41	1.23	1.11	0.28	0.67	0.90	0.47
1	1.16	0.59	0.61	0.66	1.20	0.88	0.64	0.55	0.79	0.26
2	0.59	0.81	1.06	0.48	0.87	0.83	1.06	0.48	0.77	0.23
3	0.55	0.55	0.67	—	0.85	0.80	0.53	0.48	0.63	0.14
4	0.88	0.27	0.74	0.89	0.82	0.96	0.72	0.63	0.74	0.22
5	0.26	0.70	0.61	—	0.79	0.63	0.73	0.67	0.63	0.17
6	0.97	0.59	0.55	0.90	0.42	1.14	—	0.65	0.75	0.26
7	0.95	0.59	0.49	0.52	0.42	0.53	0.53	0.52	0.27	0.16
8	0.87	0.36	0.51	0.89	0.41	0.71	0.48	—	0.60	0.22
9	0.98	0.66	1.33	0.58	0.49	1.00	0.93	0.67	0.83	0.28
10	0.50	0.15	0.67	0.63	0.29	0.40	0.56	0.25	0.43	0.19
12	0.34	0.04	—	1.50	0.43	1.00	0.33	0.33	0.57	0.50
15	0.21	0.28	—	1.09	1.67	0.00	0.09	1.00	0.62	0.63
24	0.00	0.29	—	0.5	0.75	—	—	—	0.39	0.32
Individual Mean	0.78	0.47	0.76	0.75	0.86	0.77	0.53	0.57		
SD	0.50	0.22	0.27	0.32	0.54	0.32	0.30	0.18		
CV, %	64	47	36	43	63	42	57	32		

[a] After administration of a 60-mg isosorbide dinitrate sustained-release formulation.

terminal half-lives was obtained by exponential regression analysis. Possible differences in the terminal half-lives and the times to peak saliva and plasma concentration were analyzed by paired Student's *t* test. The mean course of absorption of isosorbide dinitrate into saliva and plasma was determined by a previously described method (20).

RESULTS

Isosorbide dinitrate concentrations were measured in 111 saliva–plasma paired samples. The calculated saliva–plasma concentration ratios are listed in Table I. In 15 of the sample pairs, the measured saliva concentrations exceeded the plasma concentrations; in 92 cases the plasma levels of isosorbide dinitrate were higher than the corresponding saliva levels. The overall arithmetic mean of the saliva–plasma ratio was 0.68 ± 0.37 (*SD*). The correlation between plasma and salivary concentrations of isosorbide dinitrate for all individual values is shown in Fig. 1. The proportionality factor relating plasma to saliva concentrations was 0.60 and the correlation coefficient was 0.83. The analysis of variance of the regression revealed that 68.57% of the variation was explained by linear regression and that this was significant at the 1% level ($p < 0.01$). The 95% confidence interval for the coefficient of regression ranged between 0.52 and 0.68. The overall geometric mean for the saliva–plasma ratios was 0.61. This value corresponds well with the mean saliva–plasma ratio obtained from the regression analysis.

The individual means for the saliva–plasma ratios (Table I) ranged from 0.47 to 0.86. The corresponding coefficients of variation indicate that the extent of correlation varied between the eight volunteers. Examples of both poor and good correlations between saliva and plasma concentrations are shown in Fig. 2. The arithmetic means and standard deviations of the saliva–plasma ratio for each sample time are also given in Table I. A tendency for a decrease in the ratio with time occurred; however, the regression analysis of saliva–plasma ratios *versus* time did not show a significant correlation ($p > 0.05$). Furthermore, the correlation between the saliva–plasma ratio and absolute plasma concentration was not significant ($p > 0.05$).

Mean saliva and plasma concentrations of isosorbide dinitrate and the corresponding coefficients of variation are given in Table II. Variances between individuals in isosorbide dinitrate levels were similar in both plasma and saliva specimens. Up to 9 hr after drug intake, the coefficient of variation was 50% and, thereafter, increased to >100%.

At all sampling times, the mean concentration of drug in the plasma exceeded that found in the saliva. The saliva and plasma concentration–time curves were approximately parallel. Due to the relatively high variances both in saliva and in plasma concentrations, the observed mean saliva and plasma levels are significantly different only at the 2, 3, 5, 7, and 8 hr time intervals (paired Student's *t* test, $p < 0.05$).

The mean area under the concentration–time curve was 44.7 ± 20.4 (*SD*) hr ng/ml in saliva and 71.4 ± 39.0 hr ng/ml in plasma, corresponding to a saliva–plasma ratio of 0.63. Mean time to peak and mean apparent terminal half-life were estimated as the average of the individual calculated values. In saliva a mean peak time of 2.6 ± 2.2 hr and in plasma a mean peak time of 3.5 ± 1.4 hr were obtained. The terminal half-life was 3.0 ± 1.2 hr in saliva and 3.7 ± 1.9 hr in plasma. For both parameters, the mean difference between saliva and plasma was not significant (Student's *t* test, $p > 0.05$).

To assess the absorption characteristics of isosorbide dinitrate fol-

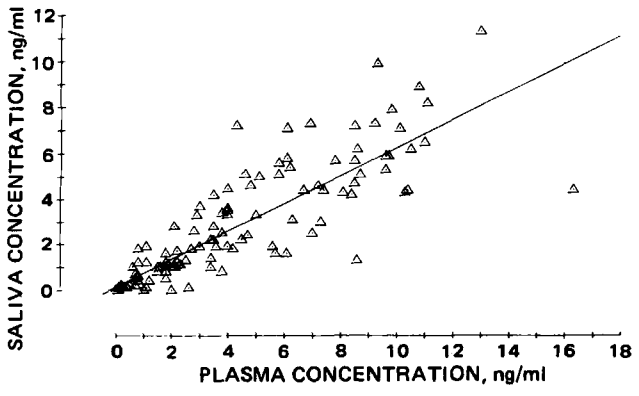

Figure 1—*Regression line for the correlation between saliva and plasma isosorbide dinitrate concentrations observed after administration of a 60-mg isosorbide dinitrate sustained-release formulation: c(saliva) = 0.60 × c(plasma) + 0.28;* r = *0.83.*

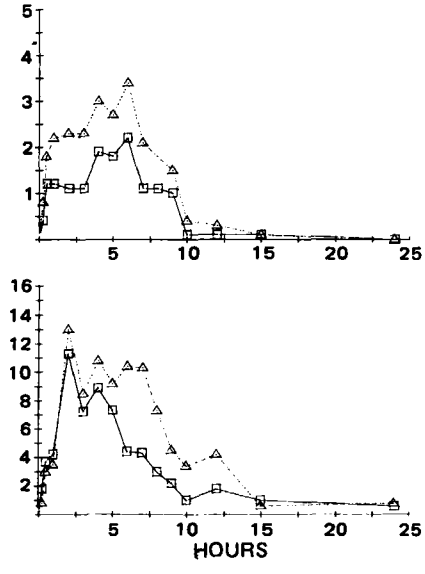

Figure 2—*Examples of different degrees of correlation between saliva (□) and plasma (△) isosorbide dinitrate concentrations in two subjects after administration of a 60-mg isosorbide dinitrate sustained-release formulation.*

Table II—Mean Isosorbide Dinitrate Concentrations in Saliva and Plasma[a]

Time, hr	Saliva Concentrations, ng/ml			Plasma Concentrations, ng/ml		
	Mean	CV, %	n	Mean	CV, %	n
0.25	1.1	73.6	6	1.3	38.4	8
0.50	3.6	58.1	8	4.2	36.7	8
1.00	4.3	44.0	8	5.6	47.5	8
2.00	6.1	60.8	8	7.5	50.5	8
3.00	4.4	44.9	7	6.5	45.5	8
4.00	5.3	44.0	8	8.0	56.6	8
5.00	4.3	56.7	8	7.0	42.7	7
6.00	4.4	33.8	7	6.7	48.9	8
7.00	2.8	65.0	8	5.0	61.5	8
8.00	2.2	71.0	8	4.3	63.7	7
9.00	2.3	61.2	8	3.0	57.6	8
10.00	1.3	101.7	8	3.3	100.6	8
12.00	0.9	87.2	8	2.1	98.3	7
15.00	0.5	85.0	8	1.2	104.6	7
24.00	0.1	186.7	8	0.5	138.5	7

[a] After administration of a 60-mg isosorbide dinitrate sustained-release formulation.

lowing ingestion of the administered slow-release formulation, absorption curves were constructed from both the experimental mean saliva curve and the mean plasma curve. For the calculation a mean elimination rate constant of 0.071 min^{-1} was employed, which was observed in plasma of human volunteers after intravenous administration of isosorbide dinitrate (10). The Wagner–Nelson curves (20) are given in Fig. 3. For comparison, in the same figure absorption curves of two standard formulations of isosorbide dinitrate are shown. These curves are reproduced from mean plasma levels obtained in other pharmacokinetic trials in which 5 and 20 mg isosorbide dinitrate were administered as plain tablet formulations to healthy human volunteers (this report will be published separately). During the first 6 hr after administration of the sustained-release formulation, the mean absorption curve calculated from isosorbide dinitrate saliva concentrations increased slightly more rapidly than the plasma absorption curve. This specimen-related difference is only marginal compared with the formulation-related differences: in contrast to the slow absorption of isosorbide dinitrate from the sustained-release preparation, the Wagner–Nelson curves (20) of the plain tablets show a steep initial increase.

DISCUSSION

The saliva–plasma ratio of drugs is influenced by many factors relating to the physicochemical characteristics of the drug and the mechanism of its salivary excretion, as well as to variable conditions such as salivary pH and flow. When a drug enters the saliva through the membranes by a simple diffusion process without the contribution of active secretion, saliva could be regarded as a plasmatic ultrafiltrate. Indeed, it has been shown for a large number of drugs that the concentration in the salivary fluid reflects the fraction of free or protein-unbound drug in plasma (1–8). As free diffusion is confined to the uncharged drug molecule, corrections should be made for pH differences on both sides of the membrane for weak acids and bases (21, 22). As isosorbide dinitrate is a lipid soluble molecule that remains uncharged within the physiological pH range, a pH-dependent effect on its membrane permeation is excluded.

Following equilibrium dialysis experiments, it was concluded that isosorbide dinitrate was not extensively bound to human plasma proteins *in vitro* (23). Within a concentration range of 1–100 ng/ml, the free fraction was found to be 0.72 ± 0.12 (mean ± *SD*). This value corresponds well with both the mean saliva–plasma ratio of isosorbide dinitrate obtained by linear regression, which was 0.60 ± 0.08 (coefficient of regression ±95% confidence limits), and the arithmetic mean of the individual saliva–plasma ratios of 0.68 ± 0.37 (mean ± *SD*). Therefore, it was suggested that the principal factor relating isosorbide dinitrate saliva to isosorbide dinitrate plasma concentrations is the degree of plasma protein binding of the drug.

Since the standard deviation of the isosorbide dinitrate protein binding (±0.12) reported previously (23) reflects the variation between different subjects, the degree of isosorbide dinitrate plasma binding determined *in vitro* is less variable between individuals than the saliva–plasma ratio found in this trial (*SD* = ±0.37). Therefore, it seems unlikely that the high variabilities of isosorbide dinitrate saliva–plasma ratios could be attributed mainly to variations in the degree of plasma binding.

In 15 of the analyses, saliva levels of isosorbide dinitrate exceeded those

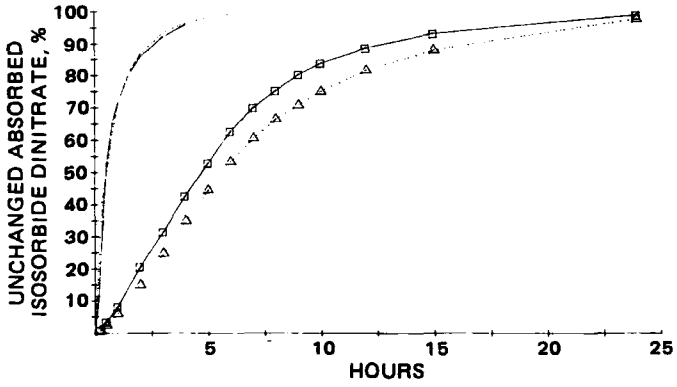

Figure 3—*Wagner–Nelson absorption curves of isosorbide dinitrate, calculated from mean isosorbide dinitrate plasma (△) and saliva (□) curves obtained after the administration of a 60-mg isosorbide dinitrate sustained-release formulation as well as after oral ingestion of a 5-mg tablet (——) and a 20-mg tablet (- - - -).*

in plasma. For some drugs [lithium is the best known example (24, 25)] saliva–plasma ratios >1 have been discussed as an indication of active transport mechanisms. It was suggested (7) that active secretion into saliva might explain the discrepancies in the saliva–plasma ratio often observed in single-dose studies, particularly when the saliva–plasma ratio appears to be time dependent. As an example, bioavailability studies for theophylline (26, 27) are reported where the saliva–plasma ratio was higher in the absorption phase than in the elimination phase and where saliva concentrations sometimes exceeded the plasma concentrations. Both phenomena were also observed for isosorbide dinitrate in the present study, so that active secretion processes should be considered as one source of the observed variation in the saliva–plasma ratios of isosorbide dinitrate.

An alternative explanation for the inconsistent ratio could be that saliva levels are influenced by isosorbide dinitrate partition into and/or absorption through the oral mucosa. As has been shown (18), the buccal absorption of isosorbide dinitrate is very rapid. Therefore, it may be possible that changes in the extent and the speed of buccal reabsorption of isosorbide dinitrate from saliva contribute considerably to the deviations in saliva–plasma ratios.

Due to the high variability of the observed saliva–plasma ratios, the prediction intervals of single plasma concentrations on the basis of corresponding saliva concentrations are considerable: the 95% confidence interval of the plasma level predicted for a saliva concentration of 5 ng/ml is 7.7 ● 3.9 ng/ml. In comparison, the mean plasma concentration of a sufficient number of subjects can be predicted with narrower confidence intervals: for eight subjects the 95% confidence interval of the mean plasma level is 7.7 ± 1.5 ng/ml. This corresponds to the observation that the mean saliva curve of isosorbide dinitrate mimics the shape of the mean plasma curve, although this does not always hold for the individual curves. Consequently, the characteristic slow-release properties of the administered formulation could be inferred from the mean saliva curve as well as from the mean plasma curve. This was particularly evident when the corresponding Wagner–Nelson absorption curves (20) were compared with the absorption curves of standard formulations of isosorbide dinitrate.

Provided these results can be confirmed for other isosorbide dinitrate preparations, it is suggested that mean saliva concentrations of a sufficient number of subjects ($n \geq 8$) can serve as a substitute for mean plasma levels in biopharmaceutical investigations of isosorbide dinitrate.

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Densitometric Determination of the Solubility Parameter and Molal Volume of Compounds of Medicinal Relevance

ZVI LIRON and SASSON COHEN ˣ

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Abstract □ A procedure is described for the simultaneous determination of molal volumes (v_2^0) and solubility parameters (δ) of compounds of medicinal interest. These include alkanoic acids of various chain length and branching (some solid at room temperature), cholesterol, and cholesteryl esters. The procedure is based on the determination of partial molal volumes ($\bar{v}_2$) from high-precision density measurements of dilute solutions of these compounds in reference solvents, which range in polarity from carbon tetrachloride (δ = 8.6) to nitrobenzene (δ = 10.0). In some cases, the present results do not agree with values of δ published in the literature. Values calculated from group contributions proposed by other authors are prone to error particularly in the case of branched acids and cholesteryl esters.

Keyphrases □ Densitometric determination—solubility parameter and molal volume of compounds of medicinal relevance □ Solubility—densitometric determination of parameters, molal volume of compounds of medicinal relevance □ Molal volume—densitometric determination of solubility parameter of compounds of medicinal relevance

In a series of studies with structurally nonspecific ethers, it was found that the pharmacological profile of a given member could be a consequence of its solubility parameter (1–3). This finding led to the proposition that such molecules associate with a particular membrane subregion, such as an ionic channel or boundary lipid, in accordance with regular solution theory (4). That is, a given substrate will partition between two phases that differ in solubility parameter at a ratio that can be predicted from the solubility parameters of the interacting species and their partial molal volumes (5). Further exploration of this concept in pharmacology and its possible application in medicinal chemistry required knowledge of reliable data pertaining to these parameters or a suitable experimental procedure for their determination. The main sources on this subject are the works of Hildebrand *et al.* (6) and reviews by Barton (7) and Burrell and Immergut (8). Although helpful, they did not meet the need because they made no reference to compounds of medicinal relevance and lack data on molal volumes, especially for solids. Therefore, this study explores the simultaneous determination of partial molal volumes and solubility parameters from high-precision density measurements of dilute regular solutions. Alkanoic acids, cholesterol, and cholesteryl esters were the compounds of choice for this exploratory study.

BACKGROUND

Definitions—The solubility parameter (δ) of a pure liquid is the square root of the cohesive energy density, and is usually given by:

$$\delta = \left(\frac{-E}{v}\right)^{1/2} = \left(\frac{\Delta H^v - RT}{v}\right)^{1/2} \text{cal}^{1/2}\,\text{cm}^{-3/2} \qquad \text{(Eq. 1)}$$

where E is the energy of the liquid expressing the molal heat of vaporization to the gas state at zero pressure, v is the molal volume of the liquid, and ΔH^v is the heat of vaporization at low vapor pressure. Under conditions of high vapor pressure, the gas law correction should be applied and ZRT should replace RT (1), Z being the compressibility factor.

If no calorimetric data are available, the Clausius–Clapeyron equation may be applied to derive the apparent heat of vaporization from pressure–temperature data:

$$\frac{d\ln P}{dT} = \frac{\Delta H^v}{RT\Delta v^v} = \frac{\Delta H^v_{app}}{RT^2} \qquad \text{(Eq. 2)}$$

where Δv^v is the change in volume on vaporization, $v^g - v^l$. The apparent heat of vaporization is equal to the true one only if the vapor is ideal. Otherwise, the compressibility factor must be used, and Eq. 1 then assumes the form:

$$\delta = \left\{\frac{(\Delta H^v_{app} - RT)Z}{v}\right\}^{1/2} \qquad \text{(Eq. 3)}$$

In the case of solid substances, application of the above relationships is not straightforward. First, many of these are nonvolatile or poorly

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