

Table: Plasma protein binding of various HIV-1 protease inhibitors

inhibitors	Protein bound share (%)
saquinavir	99 [3]
indinavir	98 [3]
DMP 323	83 [4]
DMP 450	93 [4]
H17	n.d. ^a
H19	83.23 ± 4.39*

^a n.d. = not detectable, * $\bar{x} \pm SD$, $n = 8$

tions without albumin, the protein bound share was calculated. The determined mean values are given in the Table.

H17 was found in unchanged concentrations over the tested range, H19 showed a mean protein binding of 83%. While the protein binding of H19 is low compared to peptidic HIV-1 protease inhibitors or DMP 450, H17 shows no detectable binding.

Obviously, the hydroxymethylene groups as possible functional groups for hydrophilic protein interactions are shielded by the neighbouring phenyl-substituents in the compact molecular structure as was recently derived from molecular modeling studies [11] and, additionally, proved by a low extent of phase-II metabolism of the compounds [9, 10].

Consequently, H17 shows no protein binding while in H19 the vinylogous carbamide ester moiety in certain peptidomimetic HIV-1 protease inhibitors may be the structural element decisive for binding.

In summary, protein binding of both cage or *syn* dimeric HIV-1 protease inhibitors investigated, should not be a limiting factor of their bioavailabilities which are currently determined.

Experimental

Protein binding was determined using a solution of human serum albumin (4%). For this purpose 10 ml of a solution of albumin (8%) was prepared using phosphate buffer pH = 7.4. The albumin solution was diluted with stock solutions of H17 and H19, respectively, in DMSO/buffer in terms of 1:1, so that finally 2.5 ml of each concentrations of 50, 100, 300 and 500 mg/l of the compounds were yielded. The mixtures were shaken for 2 h at 37 °C. Then the albumin was separated by a centrifugation procedure using a Zentrifugal-Ultrafilter Centriscart®. In the supernatant, concentrations of the compounds were determined UV-spectroscopically with two determinations for each concentration of H17 (254 nm) and H19 (245 nm).

Acknowledgement: Andreas Hilgeroth is grateful for the support of his work by the German Pharmaceutical Society (DPhG).

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Received January 24, 2000

Accepted March 15, 2000

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Determination of atenolol/chlortalidone during dissolution of tablets with UV multicomponent analysis

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Multicomponent pharmaceutical products are usually analyzed by HPLC. However this analysis is time-consuming, expensive and less accurate as a single UV method. Far the determination of a dissolution profile with many time intervals an automatic procedure is needed. We developed an UV method for the simultaneous determination of atenolol and chlortalidone during the dissolution of tablets with these active ingredients using the full spectrum quantitation (FSQ) from Beckman [1].

The UV spectra of the two substances are shown in Fig. 1. They are similar in the range of 220–260 nm. Maxima of atenolol are at 274 and 282 nm and maxima of chlortalidone are at 275 and 283 nm. The maxima of chlortalidone are very small in the typical concentration range of 10–25 mg/900 ml. In the range greater than 300 nm the spectra of both substances overlap and approach zero at 310 nm.

The full spectrum quantitation (FSQ), an advanced spectroscopic method for multicomponent analysis, uses principal component regression (PCR) with preprocessing in the Fourier domain of the absorbance spectrum.

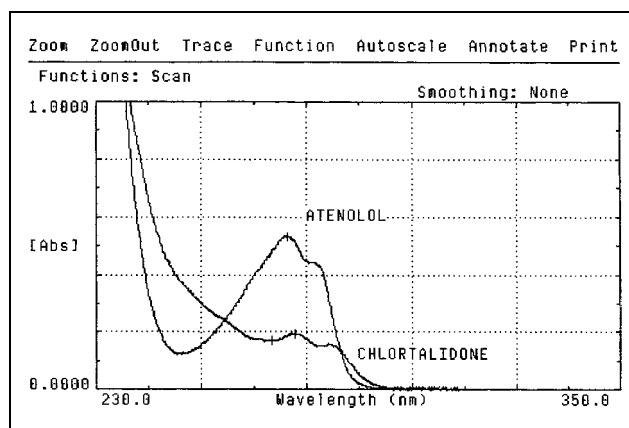


Fig. 1: UV spectra of atenolol and chlortalidone

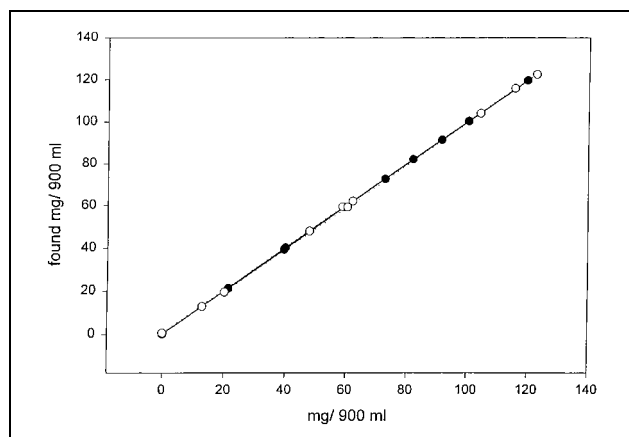


Fig. 2: Linearity of determination of chlortalidone/atenolol
—●— Atenolol, —○— Chlortalidone

We used ten independent standard mixtures to prepare the calibration matrix. The concentration range must be in the estimated range (0–120% for a dissolution procedure).

The recovery of the weighed concentrations of both substances is shown in Fig. 2. There is a good linearity in the concentration range of 0–120 mg/900 ml.

The results of Commercial product batches (tablets Evitocor[®] plus) are statistically equivalent to the results obtained by a HPLC method, but a better reproducibility was seen with the UV method.

Controls can be run to provide a quantitative representation of the validity of the calibration before running samples.

The method is secure, easy, fast, accurate and reproducible and much faster as a HPLC method. The validation parameters specificity, linearity, range, precision, accuracy and robustness according to ICH Q2B [2] show a good suitability of the method for the determination of dissolution of atenolol and chlortalidone in a pharmaceutical dosage form (tablets).

Experimental

1. Apparatus

A computerized UV/VIS-spectrophotometer (DU 640i, Beckman, USA) and a dissolution bath DT 70 (Erweka, FRG) coupled with a pump Minipuls (Gilson, France) are used. The measurement is done with a dissolution software (Beckman) and the multicomponent analysis with the FSQ-software (Beckman).

2. Drugs and reagents

Evitocor plus[®] is a product of Apogepha Arzneimittel GmbH Dresden. The tablets contain atenolol and chlortalidone as active ingredients.

3. Analytical procedure

The dissolution is determined for batch release in 5 min intervals, in the sum 30 min by UV-spectroscopy. Solvent: water 900 ml, temperature: 37°C, speed: 100 rpm, type: paddle.

The sample was pumped about filters in flow-through cells and measured with the described method using FSQ.

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Received September 7, 1999

Accepted January 15, 2000

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Solubilisation of poorly water soluble non-steroidal anti-inflammatory drugs at low pH with *N*-methylglucamine

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The objective of this study was to evaluate the solubilisation potential of *N*-methylglucamine for various non-steroidal anti-inflammatory drugs (NSAID) at low pH. The solubilising effect of *N*-methylglucamine on NSAID's represented by the arylacetic acid derivatives indomethacin and sulindac, and the arylpropionic acid derivatives naproxen, ibuprofen and ketoprofen was investigated at a pH range below the pKa values of the drugs to eliminate the effect of pH on the solubility of the drugs. The pKa values of the drugs ranged from 4.5 for indomethacin to 4.7 for sulindac. Consequently the solubility was measured at pH 3.4 and 4.2 because in this pH range the major part of the drugs is in the non-ionised insoluble form.

Previous thermodynamic and kinetic investigations of the behaviour of aqueous solutions of NSAID's reported the dominant hydrophobicity of these compounds, showing weak acidity, low solubility and dissolution rates in water, and high o/w partition coefficients, in their acidic form [1, 2]. Several approaches for solubilisation are available including techniques such as surfactant and co-solvent addition, salt formation, complexation, solid state manipulation, and prodrug derivatisation [3]. Salt formation is one of the first approaches considered as a means of increasing drug solubility and dissolution rate [4]. The most common salts of drugs, prepared to increase solubility, are the sodium and hydrochloride salts.

For acidic compounds such as NSAID's physiologically and pharmacologically compatible salts or complexes are prepared by neutralising the acidic drugs with compatible cations from corresponding inorganic and organic bases and amino acids. Pharmaceutically acceptable salts of acidic drugs are the organic, water-soluble amines made from *N*-methylglucamine (commonly known as meglumine) [5]. *N*-methylglucamine was first synthesised in 1935 [6]. The role of this compound in the improvement of the solubility of poorly water-soluble weak acid drugs is well known [7]. Its use in pharmaceuticals began with the preparation of meglumine antimonate for the treatment of Leishmaniasis. The effect of this weak amine salt on the solubility of drugs like salicylic acid, couvemyacin A, ibuprofen and other NSAID's has been studied [5, 7, 8]. In all these studies improvement in the aqueous solubility was attributed to salt formation.

The graphical illustration of the maximum concentration of the drug as a function of *N*-methylglucamine concentration at pH 3.4 (Fig. 1) and pH 4.2 (Fig. 2) reveals the existence of nearly linear relationships (mean $R^2 = 0.977 \pm 0.023$) at concentrations of *N*-methylglucamine below 0.150 M. The concentration up to where the increase in solubility was linear was estimated from plots of an adjusted correlation coefficient against concentration as described by De Villiers et al. [9]. This phenomenon is associated with 1:1 complex formation [10].

At concentrations above 0.15 M and at pH 3.4 a non-linear increase in solubility of the arylpropionic acid derivatives was observed (Fig. 1). If the solubility increased lin-