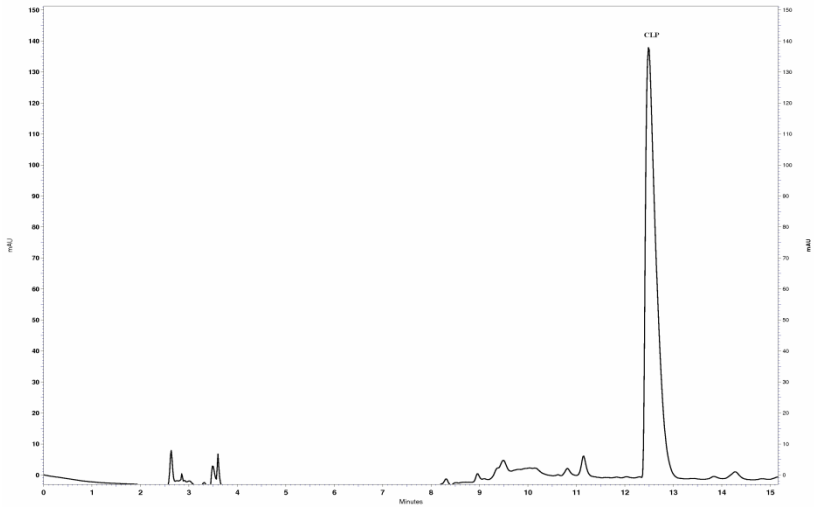
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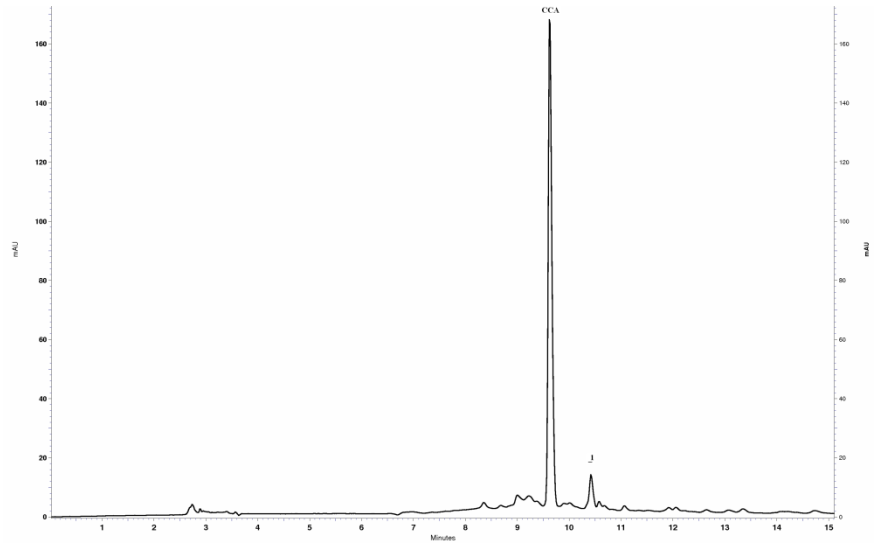
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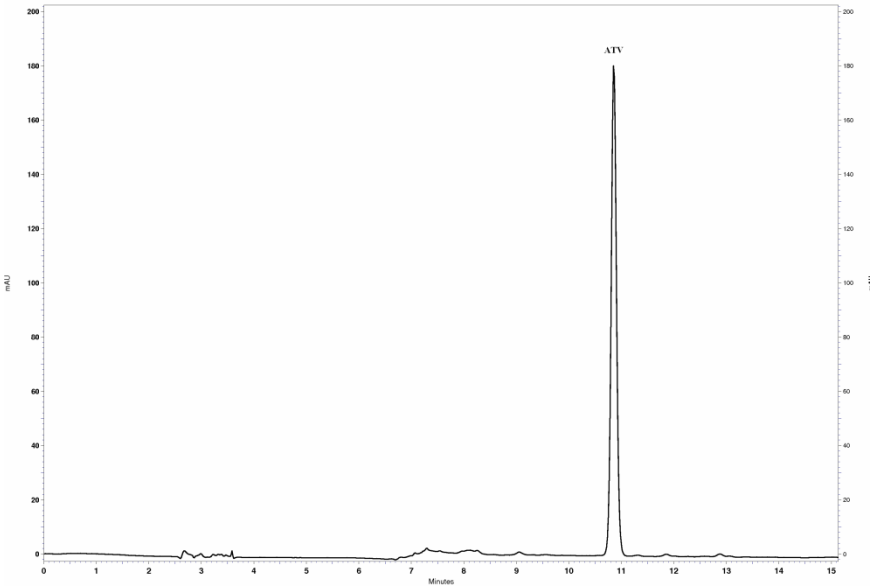
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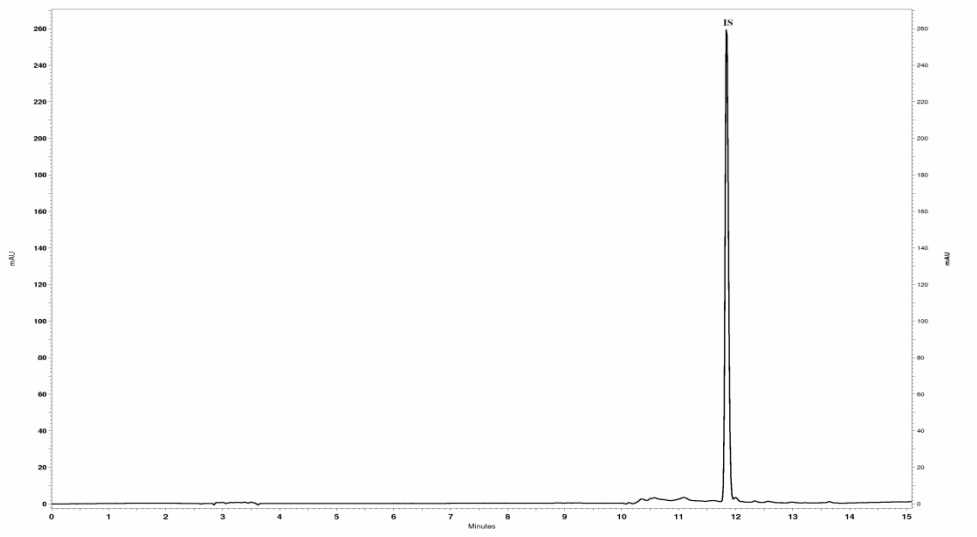

Figure S1 Chromatograms of clopidogrel bisulfate, its carboxylic acid metabolite, atorvastatin calcium and ibuprofen (IS) stock solution under the optimized chromatographic method

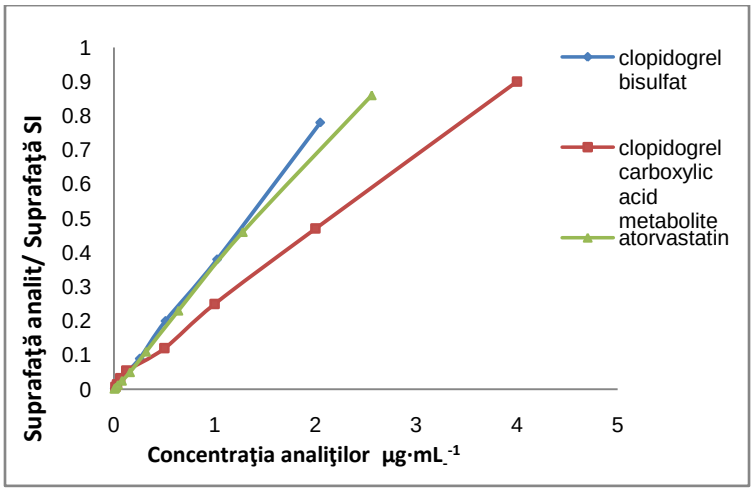

Figure S2 *Calibation curves of clopidogrel bisulfate, its carboxylic acid metabolite and atorvastatin*

Table S1 Results of calibration curves (n=3)

Method	Analyte	Range (µg/mL)	Regression ecuation	r^2
HPLC gradient method, I.S.- ibuprofen (2µg/mL)	Clopidogrel bisulfate	0.008-2	y=0.3789 x+0.0004	0.9998
	Clopidogrel carboxylic acid	0.01-4	Y=0.2227 x+0.0158	0.9995
	Atorvastatin	0.005-2.5	Y=0.3404 x+0.0017	0.9994

Pharmacokinetic parameters

Pharmacokinetic parameters are derived from data by mathematical calculations[1].

The overall absorption process is considered to be a single first order process.

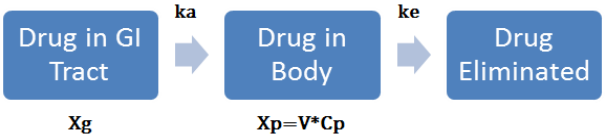

Figure X. Representing Oral Administration, One Compartment Pharmacokinetic Model

Where Xg is the amount of drug to be absorbed, Xp is the amount of drug in the body, ka is the first order absorption rate constant, ke is the elimination rate constant.

$$\frac{dXg}{dt} = -ka * Xg$$

Equation 1 Differential Equation for Amount Remaining in GI Tract

$$\frac{dXp}{dt} = ka * Xg - ke * Xp$$

Equation 2 Differential Equation for Amount of Drug in the Body

The integrated equation for Cp versus time is shown in Equation 3.

$$(Cp)t = \frac{F * Dose * ka}{V * (ka - ke)} * \left(e^{-ke*t} - e^{-ka*t}\right)$$

Equation 3 Drug Concentration after an Oral Dose

Where F is the fraction of the dose absorbed, V is the apparent volume of distribution

$\frac{F*Dose*ka}{V*(ka-ke)}$ is the intercept of the plasma drug concentration versus time plot and its slope is $\frac{-ke}{2.303}$.

The terminal slope is then back-extrapolated to the concentration axis. By means of the method of residuals we subtract the observed concentrations on the upswing of the curve (called absorption phase) from the extrapolated line.

Applying the method of residuals, the plot of the difference between extrapolated and observed plasma concentrations against time, on semilogarithmic, should yield a straight line which allows determination of the first-order absorption rate constant, using the equation

ka=-slope*2.303

[1] Mohsen A. Hedaya. *Basic Pharmacokinetics* 2nd edition. 2012. Chapter 6 Extravascular routes of drug administration, pp. 105-126

Equation 4 Absorption rate constant

The equation for the time of peak can be derived by setting the rate of change of Cp versus time, dCp/dt, to zero:

$$t_{max}=\frac{1}{(ka-ke)} * \ln(\frac{ka}{ke})$$

Equation 5 Time of Peak Concentration after an oral dose

The peak plasma concentration $(Cp)_{max}$ occurs when time is equal to t_{max}.

Area under the concentration-time curve from time zero to time t (AUC_{0-t}), where t is the last measurable time, was calculated by trapezoidal rule:

Area under the concentration-time curve from time zero to time infinity ($AUC_{0-\infty}$) was calculated with the formula:

$$AUC_{0-\infty}= AUC_{0-t} + \frac{Ct}{ke}$$

Where Ct is the last measurable drug concentration.