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Development and Validation of analytical methods for Simultaneous Estimation of Domperidone and Esomeprazole Magnesium in Bulk and in Pharmaceutical Formulations using UV-visible Spectroscopy

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Abstract: Four simple spectrophotometric methods have been developed for simultaneous estimation of Domperidone and Esomeprazole Magnesium from capsule dosage form. First method, Simultaneous equation method, involves the measurement of absorbances at two wavelengths 286.0 nm (λmax of Domperidone) and 301.0 nm (λmax of Esomeprazole Magnesium), Second method is Q-analysis method/absorption ratio method using two wavelengths, 290 nm (isobestic point at which both the drugs exhibit absorbance) and 301 nm (λmax of Esomeprazole Magnesium). Third method is Area under curve method, area under curve in the range of 276.0-290.0 nm (for Domperidone) and 292.0-310.0 nm (for Esomeprazole Magnesium) were selected for the analysis. Fourth method is First order derivative spectroscopy, the absorbance was measured at λmax =275.0 nm, λmin=288.5 nm & Zero cross=284.0nm for Domperidone and λmax =291.5 nm, λmin=313.0 nm & Zero cross=302.0 nm for Esomeprazole Magnesium respectively. Linearity for detector response was observed in the concentration range of 15-40µg/ml & 1-5µg/ml for Domperidone and Esomeprazole Magnesium respectively. The accuracy and precision of the methods were determined and validated statically. All the methods showed good reproducibility and recovery with % RSD less than 1. The proposed methods were found to be rapid, specific, precise, accurate and can be successfully applied for the routine analysis of Domperidone and Esomeprazole Magnesium in bulk and combined dosage form

Keywords: Domperidone, Esomeprazole Magnesium, Simultaneous equation method, Q-analysis, First order derivative spectroscopy, Area under curve method

Introduction:

(S)-Esomeprazole Magnesium (ESOMG) (Fig. 1) is chemically bis(5-methoxy-2-[(S)-[(4-methoxy-3,5-dimethyl-2pyridinyl)methyl]sulfinyl]-1-H-enzimidazole-1-yl),a compound that inhibits gastric acid secretion.[1,2] (S)-Esomeprazole Magnesium is cost effective in the treatment of gastric oesophageal reflux diseases. It is S-isomer of omeprazole and is the first single optical isomer proton pump inhibitor. It provides better acid control than current racemic proton pump inhibitors and has a favourable pharmacokinetic profile relative to omeprazole. Domperidone (DOM) (Fig. 1), a dopamine antagonist is usually given along with proton pump inhibitors as ulcers are usually attended with vomiting. Chemically, it is [5-chloro-1-[1,3-(2,3-dihydro-2-oxo-1H-benzmidazole-1yl)propyl)-4-piperdinyl-1,3-dihydro-2H-benzimidazole-2-one].[3,4]

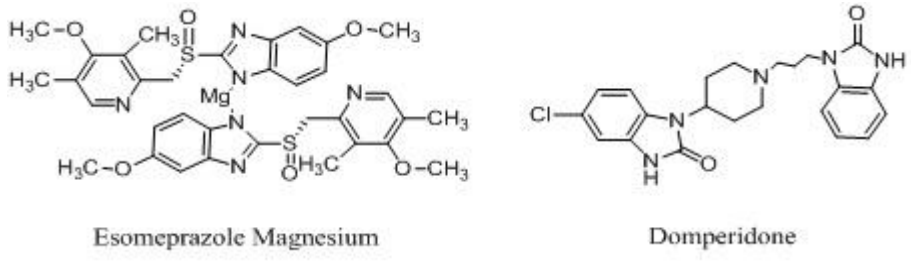

Fig. 1. Chefmical structure of Esomeprazole Magnesium and Domperidone

A detailed survey of literature revealed the estimation of ESOMG by gas chromatographic method[4], UV spectrophotometric method[5–6], TLC[7] and several HPLC[8–20] methods. Estimation of DOM included spectrophotometric methods[21–22], HPLC[23–26] and HPTLC[27] in dosage forms. Combination of these two is used for the treatment of gastric esophagus reflux disease.

Materials and Methods:

A double-beam UV-Visible spectrophotometer, model UV-1800 (Shimadzu, Japan) having two matched cells with 1-cm light path. A Citizen analytical balance (Sartorius) was used for weighing the samples. Esomeprazole Magnesium was gifted from RMS Research Labs, Hyderabad, India and Domperidone was gifted from Vasudha pharmaceuticals Ltd, Andhra Pradesh, India. All other chemicals and solvents used were of analytical grade.

Preparation of standard stock solutions: Standard stock solutions of ESOMG and DOM were prepared separately by dissolving 10 mg of each drug in 10ml of methanol to get standard stock solution of 1000 µg/ml respectively and 1 ml was pipette out and further volume was made up to 10 ml with methanol to obtain concentration of 100 µg/ml. Further dilutions were made in distilled water from stock solution to get concentrations of 1-5µg/ml of ESOMG & 15-40 µg/ml of DOM.

Determination of Absorption Maxima: Accurately weighed DOM (10 mg) and ESOMG (10 mg) were transferred to a 10 mL volumetric flask, dissolved in methanol and diluted to 10 mL with water. The solution (1mL) was transferred to a 10 mL volumetric flask and diluted up to the mark with water to obtain final solution of DOM (100 µg/mL) and ESOMG (100 µg/mL). The working standard stock solutions of DOM and ESOMG were scanned in the range of 200 to 400 nm against methanol as a blank. The absorbance of each solution was measured at both the wavelengths 286.0 nm and 301.0 nm. Iso-absorptive point was found at 290 nm Another wavelength used is 301 nm which is lambda-max of ESO. (Fig. 2)

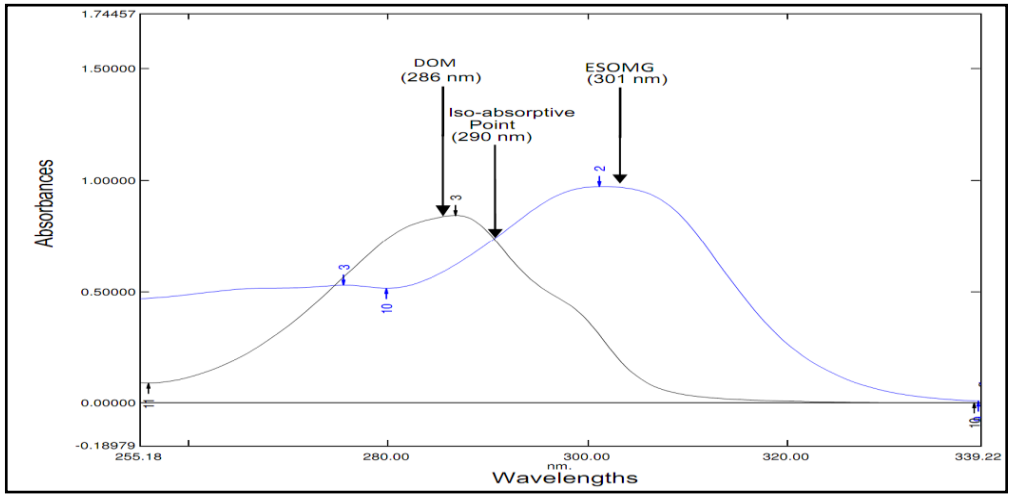

Fig 2: Overlain Spectra of DOM and ESOMG Showing Isobestic Point

Simultaneous Equation Method (Method I): From the stock solution (10 ug/mL), working standard solutions of drugs were prepared by appropriate dilution and were scanned in entire UV range to determine the λmax.

Standard solutions were prepared having concentration (15-40 ug/mL and 1-5 ug/ml) for DOM and ESOMG. The absorbances of these standard solutions were measured at 286.0 nm and 301.0 nm and calibration curves were plotted. Two simultaneous equations (in two variables Cx and Cy) were formed using these absorptivity coefficient values. (Fig. 2)

A1 = 0.84337Cx + 0.8414Cy---------- (i)
A2 = 0.97263Cx + 0.97314Cy---------- (ii)
Where, Cx and Cy are the concentration of DOM and ESOMG measured in µg/mL, in sample solutions. A1 and A2 are the absorbance of mixture at 286.0 nm and 301.0 nm wavelength respectively. By applying the Cramer's rule to equation i and ii, the concentration C_{DOM} and C_{ESOMG}, can be obtained as follows,

$$C_{DOM} = \frac{A2\ (0.8414) — A1\ (0.97314)}{0.0023462}$$

$$C_{ESOMG} = \frac{A1\ (0.97263) — A2\ (0.84337)}{0.0023462}$$

Q-Analysis Method (METHOD II): In this method absorbance are measured at two wavelengths. One being the λmax of DOM and other being a wavelength of absorptivity of the ESOMG. Then absorbance of both drugs was recorded on selected wavelengths. Concentrations of DOM & ESOMG were calculated by using following equations.

$$C_{DOM} = [(1.283238 — 0.738445)/ (0.779279 — 0.738445)] \times A1 /0.75795 \ldots\ldots\ldots\ldots\ldots (iii)$$

$$C_{ESOMG} = [(1.283238 — 0.779279)/ (0.738445 — 0.779279)] \times A1/0.71861 \ldots\ldots\ldots\ldots\ldots (iv)$$

Where, Qm is ratio of absorbance A1 and A2 of mixture at λ_1 and λ_2 (Isobestic Point wavelength) Qx is ratio of absorptivities ax_1 and ax_2 at λ_1 and λ_2. Qy is ratio of absorptivities ay_1 and ay_2 at λ_1 and λ_2. C_{DOM} and C_{ESOMG} are concentrations of DOM and ESOMG. (Fig. 2)

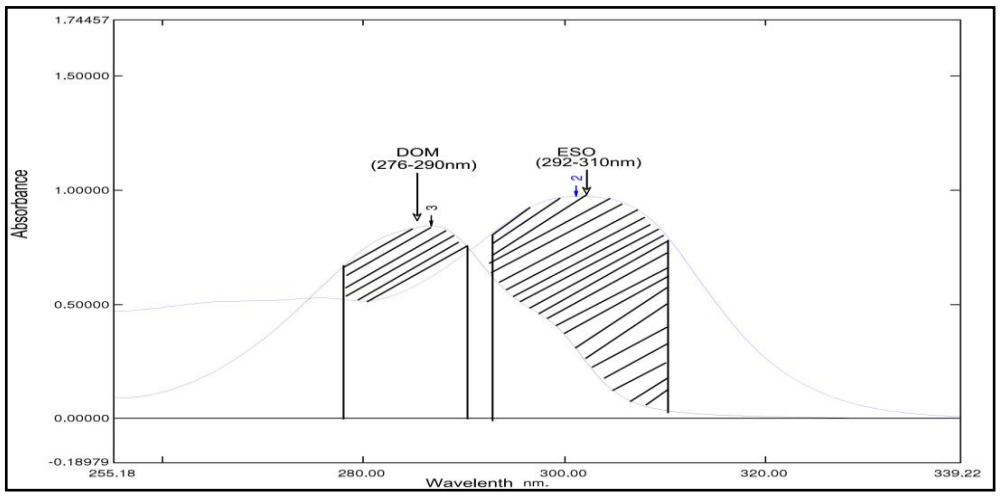

Fig. 3: Ovrelay of DOM and ESOMG Showing Area Under Curve

Area under curve method (Method III): From the overlain spectra of both drugs (Fig. 3), area under the curve in the range of 276.0-290.0 nm (for DOM) and 292.0-310.0 nm (for ESOMG) were selected for the analysis. The calibration curves for DOM and ESOMG were prepared in the concentration range of 15-40 ug/ml and 1-5 ug/mL at their respective AUC range. The 'X' values of the drugs were determined for both the drugs at the selected AUC range. The 'X' is the ratio of area under the curve at selected wavelength ranges with the concentration of component in gm/lit. These 'X' values were the mean of six independent determinations. A set of two simultaneous equations obtained by using mean 'X' values are given below.

Where,

$$C_{DOM} = \frac{[X^{ESOMG}_{(276.0\text{-}290.0)} \times AUC_{(292.0\text{-}310.0)}] - [X^{ESOMG}_{(292.0\text{-}310.0)} \times AUC_{(276.0\text{-}290.0)}]}{[X^{ESOMG}_{(276.0\text{-}290.0)} \times X^{DOM}_{(292.0\text{-}310.0)}] - [X^{ESOMG}_{(292.0\text{-}310.0)} \times X^{DOM}_{(276.0\text{-}290.0)}]} \quad \ldots\ldots\ldots (v)$$

$$C_{ESOMG} = \frac{[X^{DOM}_{(276.0\text{-}290.0)} \times AUC_{(292.0\text{-}310.0)}] - [X^{DOM}_{(292.0\text{-}310.0)} \times AUC_{(276.0\text{-}290.0)}]}{[X^{ESOMG}_{(276.0\text{-}290.0)} \times X^{DOM}_{(292.0\text{-}310.0)}] - [X^{ESOMG}_{(292.0\text{-}310.0)} \times X^{DOM}_{(276.0\text{-}290.0)}]} \quad \ldots\ldots\ldots (vi)$$

C_{DOM} and C_{ESOMG} are concentration of DOM and ESOMG respectively.

$AUC_{(276.0\text{-}290.0)}$ and $AUC_{(292.0\text{-}310.0)}$ are area under curve of solution at wavelength range between 276.0-290.0 nm and 292.0-310.0 nm. $X^{ESOMG}_{(276.0\text{-}290.0)}$, $X^{ESOMG}_{(292.0\text{-}310.0)}$; $X^{DOM}_{(276.0\text{-}290.0)}$, $X^{DOM}_{(292.0\text{-}310.0)}$ are absorptivities of DOM and ESOMG at respective wavelengths.

First order derivative spectroscopy (Method IV): In this method solutions of DOM (15-40 ug/ml) and and ESOMG(1-5 ug/mL), were prepared separately by appropriate dilution of standard stock solution and scanned in the spectrum mode from 400 nm to 200 nm. The absorption spectra thus obtained were derivatized from first to fourth order. First order derivative spectra were selected for analysis of both drugs. From the overlain spectra of both drugs (Fig. 4), the absorbance was measured at λmax =275.0 nm, λmin=288.5 nm & Zero cross=284.0nm for Domperidone and λmax =291.5 nm, λmin=313.0 nm & Zero cross=302.0 nm for Esomeprazole Magnesium respectively amplitude difference was measured for the respective concentration of standard and was plotted against concentration and regression equation was calculated.

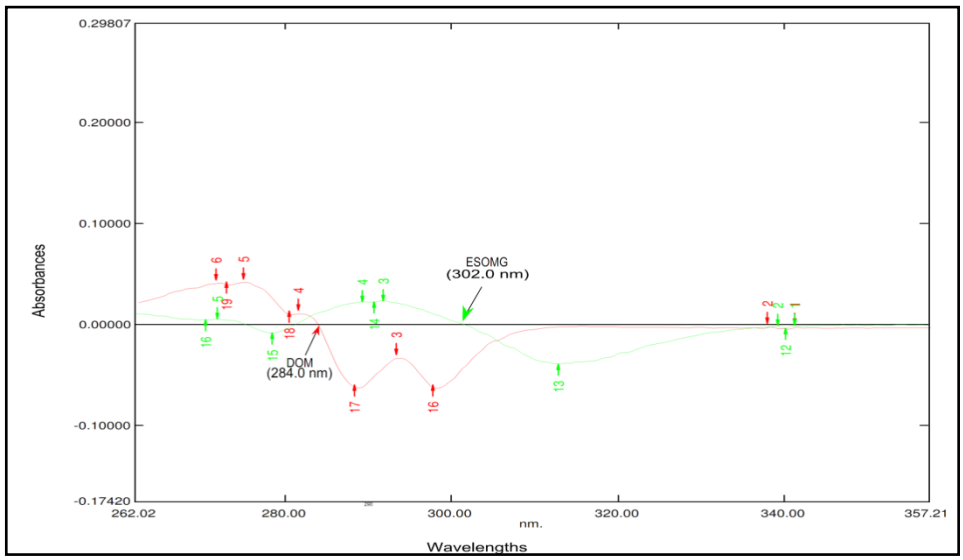

Fig 4: Overlain First Derivative Spectra of DOM and ESOMG

Application of the proposed methods for the determination of DOM and ESOMG in commercial formulation

The powder of 20 capsules was weighed, mixed and accurately a quantity of the powder equivalent to about 30 mg of DOM and 20 mg of ESOMG is transferred in to 100 mL measuring flask. The solution was filtered through Whatman filter paper No. 41 and the residue was washed thoroughly with methanol. After rejecting first few ml, different concentrations of capsule sample were prepared by serial dilution technique with distilled water. Absorbance of sample solutions were recorded at 286.0 nm and 301.0 nm and the concentration of two drugs in the sample were determined by using eqns. i and ii (Method-I).

The Absorbance of sample solutions were recorded at wavelengths, 290 nm (Isobestic point at which both the drugs exhibit absorbance) and 301 nm (λmax of ESOMG). The concentration of two drugs in the sample were determined by using eqns. iii and iv (Method-II).

For Method-III, the concentration of both DIA and ACE were determined by measuring area under curve in the range of 276.0-290.0 nm (for DOM) and 292.0-310.0 nm (for ESOMG) and values were substituted in the respective formula to obtain concentrations. The analysis procedure was repeated for 6 times with Capsule formulations.

The concentration of both DOM and ESOMG were determined by measuring at λmax =275.0 nm, λmin=288.5 nm & Zero cross=284.0nm for DOM and λmax =291.5 nm, λmin=313.0 nm & Zero cross=302.0 nm for ESOMG respectively. The results of the Capsule analysis were calculated against the calibration curve in quantitation mode (Method IV). The results are reported in Table. 1.

Table No. 1: Results of Analysis of Capsule Formulation

Method	Capsule content	Label claim (mg/tab)	Amount Found*		±SD	RSD %
			(in mg)	(in %)		
I	DOM	30	29.8617	99.5389	0.0763	0.2554
	ESOMG	20	19.9898	99.8912	0.1019	0.5099
II	DOM	30	30.0083	100.0278	0.0732	0.2440
	ESOMG	20	19.1235	99.2827	0.0851	0.4451
III	DOM	30	30.0067	100.0222	0.0830	0.2767
	ESOMG	20	20.0330	100.1651	0.0950	0.4744
IV	DOM	30	29.9750	99.9167	0.1153	0.3847
	ESOMG	20	20.0223	100.1114	0.1173	0.5858

*denotes n = 6, average of six determinations; DOM: Domperidone; ESOMG: Esomeprazole Magnesium

Validation

The methods were validated with respect to linearity, accuracy, precision and selectivity.

Accuracy

To ascertain the accuracy of the proposed methods, recovery studies were carried out by standardaddition method at three different levels 80%, 100% & 120% (Table 2). The mean percent recovery for DOM and ESOMG by all the three methods was found in the range of 99.39 % to 100.31%

Table 2: Result of Recovery Studies

Level of recovery	Drug	Amt of Drug added µg/ml	Amt of drug std added µg/ml	METHOD I		METHOD II		METHOD III		METHOD IV	
				% Recovery	SD	% Recovery	SD	% Recovery	SD	% Recovery	SD
80%	ESOMG	20	19.78	99.16%	0.1667	98.93%	0.0112	99.93%	0.0583	98.93%	0.0361
	DOM	30	29.93	99.00%	0.7092	100.12%	0.0342	100.02%	0.0739	99.16%	0.0757
100%	ESOMG	20	19.83	99.40%	0.3838	99.39%	0.2421	99.86%	0.0813	99.78%	0.4092
	DOM	30	29.95	99.29%	0.6554	98.12%	0.0642	99.75%	0.0262	99.86%	0.3838
120%	ESOMG	20	19.93	99.78%	0.3886	99.96%	0.0761	100.31%	0.0611	99.00%	0.2113
	DOM	30	29.98	99.89%	0.4421	100.32%	0.0757	99.97%	0.0975	100.31%	0.0342

*Mean of six estimations; DOM: Domperidone; ESOMG: Esomeprazole Magnesium

Linearity

The six-point calibration curves that were constructed were linear over the selected concentration range for both DOM and ESOMG ranging between 15-40ug/ml and 1-5ug/mL. Each concentration was repeated 3 times. The assay was performed according to the experimental conditions previously described. The linearity of the calibration graphs and adherence of the system to Beer's law were validated by the high value of the correlation coefficient and the intercept value.

Precision

The reproducibility of the proposed method was determined by performing Capsule assay at different time intervals (morning, afternoon and evening) on same day (Intraday assay precision) and on three different days (Interday precision). Result of intraday and interday precision is expressed in % RSD (Table 3). Percent RSD for Intraday assay precision was found to be 0.0690 (for DOM) and 0.0197 (for ESOMG) in simultaneous equation method; 0.0781 (for DOM) and 0.3698 (for ESOMG) in Q-Analysis Method; 0.6198 (for DOM) and 0.4568 (for ESOMG) in area under the curve method and 0.2375 (for DOM) and 0.0561 (for ESOMG) in First derivative spectrophotometric method. Interday assay precision was found to be 0.5186 (for DOM) and 0.2662 (for ESOMG) in simultaneous equation method; 0.3743 (for DOM) and 0.3166 (for ESOMG) in Q-Analysis Method; 0.2681 (for DOM) and 0.1375 (for ESOMG) in area under the curve method and 0.0275 (for DOM) and 0.0281 (for ESOMG) in First derivative spectrophotometric method.

Table No. 3: Results of Intermediate Precisions

Day	METHOD I		METHOD II		METHOD III		METHOD IV	
	% Label claim estimated* (Mean ± % R.S.D.)		% Label claim estimated* (Mean ± % R.S.D.)		% Label claim estimated* (Mean ± % R.S.D.)		% Label claim estimated* (Mean ± % R.S.D.)	
	DOM	ESOMG	DOM	ESOMG	DOM	ESOMG	DOM	ESOMG
Intra day	30.0193± 0.0690	19.9840± 0.0197	29.1093± 0.0781	19.7844± 0.3698	30.0243± 0.6198	19.9940± 0.4568	29.1012± 0.2375	19.9293± 0.0561
Inter day	30.1083± 0.5186	19.9920± 0.2662	30.9393± 0.3743	19.9880± 0.3166	29.9403± 0.2681	19.8990± 0.1375	30.1909± 0.0275	19.9981± 0.0281

Results and Discussion:

The methods discussed in the present work provide a convenient and accurate way for simultaneous analysis of DOM and ESOMG. In simultaneous equation method, wavelength selected for quantitation were 286.0 nm (λmax of DOM) and 301.0 nm (λmax of ESOMG). In Q-analysis method/absorption ratio method, selected for quantitation were, 290 nm (isobestic point at which both the drugs exhibit absorbance) and 301 nm (λmax of Esomeprazole Magnesium).In area under curve method, the area under curve in the range of 276.0-290.0 nm (for DOM) and 292.0-310.0 nm (for ESOMG) were selected for the analysis. In first order derivative spectroscopy, at λmax =275.0 nm, λmin=288.5 nm & Zero cross=284.0nm for DOM and λmax =291.5 nm, λmin=313.0 nm & Zero cross=302.0 nm for ESOMG respectively. The optical characteristics such as Beer's law limits, and Sandell's sensitivities are presented in [Table 4]. Percent label claim for DOM and ESOMG in Capsule analysis, by all the three methods, was found in the range of 99.9167 % to 100.3324 %. Standard deviation and coefficient of variance for six determinations of Capsule sample, by all the methods, was found to be less than ± 2.0 indicating the precision of both the methods. Accuracy of proposed methods was ascertained by recovery studies and the results are expressed as % recovery. Percent recovery for DOM and ESOMG, by all the methods, was found in the range of 99.86 % - 100.36 %, values of standard deviation and coefficient of variation was satisfactorily low indicating the accuracy of both the methods. Based on the results obtained, it is found that the proposed methods are accurate, precise, reproducible & economical and can be employed for routine quality control of DOM and ESOMG in combined dose Capsule formulation.

Table 4: Validation parameters for UV-Spectroscopic methods

PARAMETERS	METHOD I		METHOD II		METHOD III		METHOD IV	
	ESOMG 301nm	DOMP 286nm	ESOMG	DOMP	ESOMG	DOMP	ESOMG	DOMP
Linearity range(µg/ml)	1-5ug/ml	15-40ug/ml	1-5ug/ml	15-40ug/ml	1-5ug/ml	15-40ug/ml	1-5ug/ml	15-40ug/ml
Correlation coefficient (r2)	0.974	0.993	0.984	0.992	0.999	0.995	0.997	0.989
Sandell's sensitivity (mcg/Sq.cm/0.001)	0.0139	0.0202	0.0386	0.0462	0.0204	0.0280	0.0362	0.0405
Slope	0.244	0.135	0.255	0.182	0.205	0.122	0.1301	1.253
intercept	0.042	0.023	0.042	0.022	0.041	0.024	0.043	0.072

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