Stability Indicating Assays Method for Simultaneous Estimation of Pregabalin and Mecobalamin in Combined Capsule Dosage form by Absorbance Ratio UV Spectrophotometric Method

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ABSTRACT-
A new UV spectrophotometric absorption ratio method was developed and validated with force degradation study for simultaneous estimation of pregabalin and mecobalamin in pharmaceutical capsule dosage form. The proposed method is simple, precise, accurate and economic developed and validated according to ICH guidelines. The wavelength (λmax) for detection of pregabalin and mecobalamin were selected as 227nm (isobestic point) and 351nm respectively. The linearity range between 15-90 μg/mL and 0.1-0.9 μg/mL obeys Beer-Lambert's law with correlation coefficient 0.999 and 0.999 for pregabalin and mecobalaminrespectively.The LOD value was 1.845 μg/mL and 0.0166 μg/mL and LOQ value was 6.151 μg/mL and 0.0503 μg/mL for pregabalin and mecobalamin respectively. The % assay was found to be 99.65±0.81 % for pregabalin and 99.43±0.66 % for mecobalamin in bulk dosage form. The degradation behavior of the pregabalin and mecobalamin were studied by subjecting to an acid, alkaline, neutral, oxidative, photolytic and thermal condition.

Keywords:UV spectrophotometry, Pregabalin, Mecobalamin, Force degradation study, Absorption ratio method.

I. INTRODUCTION

Pregabalin (PRG), (3S)-3-(aminomethyl)-5-methylhexanoic acid (Fig. 1) it is a fundamental analogue of γ-amino butyric acid[1]. It is a white to off-white crystalline solid in color. It is freely soluble in water and both basic and acidic solution. It is antiepileptic drug mainly used in neuropathic pain. Its molecular weight is 159.229 g/molandmolecular formula $C_8H_{17}NO_2$[2].
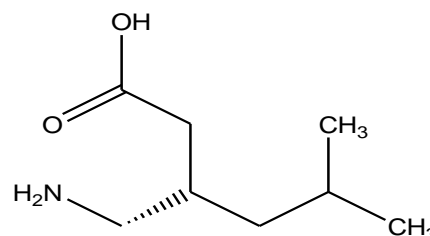

Fig. 1: Chemical structure of Pregabalin

Pregabalin is anticonvulsant drug used for neuropathic pain and as an adjunct therapy for partial seizures. Pregabalin binds with high affinity to the alpha2-delta site (an auxiliary subunit of voltage-gated calcium channels) in central nervous system tissues.Pregabalin is a structural derivative of inhibitory neurotransmitter gamma-aminobutyric acid (GABA), it does not bind directly to GABA or benzodiazepine receptors[3].

Mecobalamin (MCA) also called as cobalamin, a form of vitamin B_{12}, used in treatment of megaloplastic anemia, diabetic neuropathy and peripheral neuropathy. Its molecular formula is $C_{63}H_{91}CoN_{13}O_{14}P$ [4]. MCA structurally is Carbanide; cobalt (3+); [5-(5,6-dimethylbenzimidazol-1-yl) -4-hydroxy-2 (hydroxymethyl) oxolan-3-yl] 1-[3-[(4Z,9Z,14Z) 2,13,18-tris (2-amino-2-oxoethyl) 7,12,17 tris (3amino-3-oxopropyl) 3,5,8,8,13,15,18,19-octamethyl 2,7,12,17 tetrahydro 1H corrin 21-id-3-yl] propanoylamino] propan-2-yl phosphate. It is a dark red crystals or an amorphous or crystalline red color powder. It is soluble in alcohol and water [5]. Its molecular weight is 1344.405 g/mol.

Mecobalamin stimulates reticulocytes, thus playing important role in hematopoiesis in that, together with folic acid, it is involved in formation of deoxyribonucleotides from ribonucleotides[6].The chemical structure of mecobalamin is show in Fig. 2.
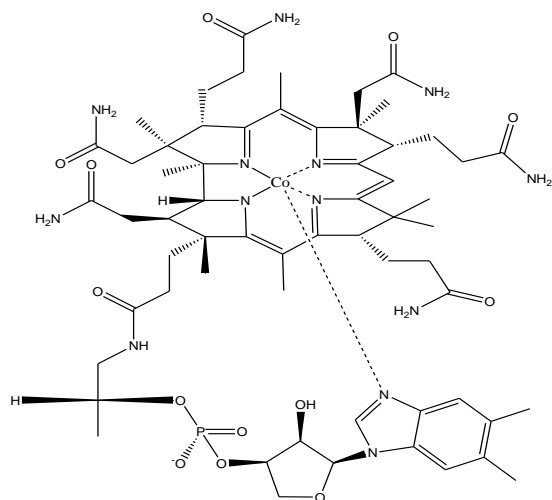
Fig. 2: Chemical structure of Mecobalamin

The literature survey revealed that HPLC[7-17], HPTLC[18], UV [19-20]and stability indicating HPLC methods reported for the estimation of pregabalin and mecobalamin individually and in combination with other drugs. According to literature survey no stability indicating UV spectrophotometric method has yet been reported for simultaneous estimation of pregabalin and mecobalamin in combination by using 0.1N HCl as solvent. The present work described stability indicating UV spectrophotometric methods for the simultaneous estimate on of pregabalin and mecobalamin by absorbance ratio method.

II. MATERIAL AND METHOD

Pharmaceutically pure sample or working standard / drug sample of pregabalin and mecobalamin was obtained as a gift sample from Zim Laboratories Ltd Pharmaceutical Company in Kalameshwar, Nagpur. The marketed formulation-PREGASTAR M 75mg Capsule 10s (Pregabalin 75mg + Mecobalamin 750mcg) Lupin Limited is available in market purchased and used for work. All other chemicals used in the analysis were Analytical grade.

Instrumentation

A double beam UV-visible spectrophotometer (Shimadzu) model UV-1800 PC was used for the determination of wavelength of both drugs. The software employed was UV probe. The spectrum was recorded over range 200-400 nm against solvent in 1 cm quarts cells. Electronic analytical balance (Anamed) model AA-2200, Ultrasonicator (HMG India) was used.

Preparation of standard stock solution

The sample equivalent to 10 mg of PRG and 1 mg of MCA are weighed separately, transferred into 100 mL volumetric flask and dissolve in 0.1N HCl. Then volume was made up to100 mL with same solvent to get a concentration of 100 µg/mL of PRG and 10 µg/mL of MCA.

Determination of absorption maxima and selection of suitable wavelength

The working standard solutions of these drugs were obtained by dilution of the above stock solution with 0.1N HCl. 1 mL of above stock solution was diluted to 10 mL to get a concentration of 10 µg/mL of PRG and 1 µg/mL of MCA use as same solvent. Both the solutions were scanned in the range 200-400 nm against 0.1N HCl use as blank.

Preparation of calibration curve

The standard stock solution is used for preparation of different dilution. The preparation of calibration curve mainly uses linearity range between 15-90 µg/mL for PRG and 0.1-0.9 µg/mL for MCA were prepared in 0.1N HCl. The absorbance of solution is measured at 227 nm and 351 nm for PRG and MCA respectively, used 0.1N HCl as blank. The calibration curve was plotted for these concentration verses absorbance value obtained at respective wavelength.

Experimental
Method:Absorbance ratio or Q-analysis method

Q-Absorbance method uses the ratio of absorbance at two selected wavelengths one at isoabsorptive point and other being the absorbance maxima of one of the two drug. PRG and MCA have absorption maxima at 210 nm and 351 nm respectively and isoabsorptive point 227 nm. The wavelength was selected for analysis was 227 nm and 351 nm for the estimation of PRG and MCA respectively.

The concentration of two drugs in the mixture can be calculated by using following equation I and II.

$Cx = Qm-Qy/ Qx-Qy \times A/ax_1$…. (I)
$Cy = Qm-Qx/ Qy-Qx \times A/ay_1$……. (II)

Were,

Cx = Concentration of PRG in gm/100mL

Cy = Concentration of MCA in 100 gm/mL

Qm = Absorbance ratio of sample at 227 nm & 351 nm

Qx = Ratio of absorptivity of PRG at 227 nm & 351 nm

Qy= Ratio of absorptivity of MCA at 227 nm & 351 nm
A= Absorbance of mixture at isoabsorptive wavelength
ax_1 & ax_2 = Absorptivity of PRG and MCA at isoabsorptive point

Method Validation:
Method was validated according to ICH guidelines.
Linearity: The linearity was determined at 6 different standard concentrations of PRG and MCA. The linearity range for PRG and MCA were found to be 15-90 µg/mL and 0.15-0.9 µg/mL respectively. Standard calibration curve was plotted between absorbance against concentration of drug. Linearity was assessed in the terms of slope, intercept and regression coefficient for both drugs.
Accuracy: Accuracy expresses the closeness of agreement between the value which is accepted either as a conventional true value or an accepted reference value and the value found. The recovery studies were carried out at 3 different concentration levels (80%, 100% and 120%) by adding a known amount of standard to preanalysed sample. Percent recovery for PRG and MCA was found in range, each determination was repeated at three times at each level.
Precision: Precision is usually expressed as the standard deviation or relative standard deviation (coefficient of variation). Precision are determine three replicate of each sample. In repeatability study the 15 µg/mL of PRG and 0.15 µg/mL of MCA concentration sample are scan repeated. In intermediate precision the sample was performed by time interval. Mainly interday precision and intraday precision was performed.

Limit of detection (LOD) and Limit of quantification (LOQ): LOD is the lowest concentration of analyte in a sample that can be detected but not necessarily quantified LOQ is the lowest concentration of analyte in the sample that can be quantitatively determined with precision and accuracy.
LOD and LOQ was calculated from linear curve using following formulas

$$LOD = 3.3\sigma/Slope,$$
$$LOQ = 10\sigma/Slope$$

(Where σ = the standard deviation of the response and S = Slope of calibration curve).
Analysis of Marketed formulation: Twenty capsule of marketed formulation was taken, weighed and average weight was determined. The powder equivalent to average weight was taken

contain 75 mg PRG and 0.75 mg MCA, in 100 ml volumetric flask. Dissolve in 0.1N HCl and sonicated for 15 min then make up the volume up to the mark with same solvent. Then filter the sample with Whatman filter paper No. 41. Finally dilution was done to get finalconcentration containing 15 µg/mL of PRG and 0.15 µg/mL of MCA use 0.1 N HCl.

Force degradation studies:
Acid hydrolysis: The accurately weighed 10 mg of PRG and 1 mg of MCA transfer in 100 mL volumetric flask and dissolve in 10 mL solvent. Then add 10 mL 0.1N HCl shake well and reflux for 1 h at $80^{\circ}C$, cool the sample at room temperature and neutralize with 0.1N NaOH. Shake the sample and make up the volume up to the mark, to get final concentration 15 µg/mLof PRG and 0.15 µg/mL of MCA. Finally absorbance of sample was compared with standard absorbance and percent degradation was calculated.
Base hydrolysis: The accurately weighed 10 mg of PRG and 1 mg of MCA transferred in 100 mL volumetric flask and dissolve in 10 mL solvent. Then add 10 mL 0.1N NaOHshake well, and reflux for 1 h at $80^{\circ}C$. Cool the sample at room temperature and neutralize with 0.1 N HCl. Then make up the volume up to the mark, to get final concentration 15 µg/mL of PRG and 0.15 µg/mL of MCA. Finally absorbance of sample was compared with standard absorbance and percent degradation was calculated.
Neutral hydrolysis: The accurately weighed 10 mg of PRG and 1 mg of MCA transferred in 100 mL volumetric flask and dissolve in 10 mL water. Reflux for 1 h at $80^{\circ}C$, cool the sample at room temperature and make up the volume up to the mark, to get final concentration 15 µg/mL of PRG and 0.15 µg/mL of MCA. Finally absorbance of sample was compared with standard absorbance and percent degradation was calculated.
Photolytic degradation: Pure drug exposed under UV light for 12 h. After exposure, the drug accurately weighs 10 mg of PRG and 1 mg of MCA transferred into 100 mL volumetric flask. The volume make up to the mark, to get final concentration 15 µg/mL of PRG and 0.15 µg/mL of MCA. Finally absorbance of sample was compared with standard absorbance and percent degradation was calculated.
Oxidative degradation: The accurately weighed 10 mg of PRG and 1 mg of MCA transferred in 100 mL volumetric flask and dissolve in 10 mL solvent. Then add 10 mLof3% hydrogen peroxide, and

shake well. Reflux for 1 h at 80°C. Cool the sample at room temperature and make up the volume up to the mark, to get final concentration 15 µg/mL of PRG and 0.15 µg/mLof MCA. Finally absorbance of sample was compared with standard absorbance and percent degradation was calculated.

Thermal degradation: Thermal degradation was carried out by exposing both pure drugs to dry heat at 80 °C for 2 h. After exposure accurately weigh 10 mg of PRG and 1 mg of MCA transferred in 100 mL volumetric flask and make up the volume up to the mark, to get finalconcentration 15 µg/mL of PRG and 0.15 µg/mL of MCA. Finally absorbance of sample was compared with standard absorbance and percent degradation was calculated.

III. RESULT AND DISCUSSION

A stability indicating UV spectrophotometric absorption ratio method was developed and validated for simultaneous estimation of pregabalin and mecobalamin in pharmaceutical capsule dosage form. The proposed method is simple, precise, accurate and economic developed and validated according to ICH guidelines. The given method solvent was used 0.1 N HCl.

The spectra of PRG and MCA show an absorbance peak at 210 nm and 351 nm of PRG and MCA respectively. The overlain spectra show iso-absorptive point at 227 nm. The wavelength (λmax) for detection of pregabalin and mecobalamin were selected as 227nm (isobestic point) and 351nm respectively. The overlain spectrum is shown in Fig. 3.
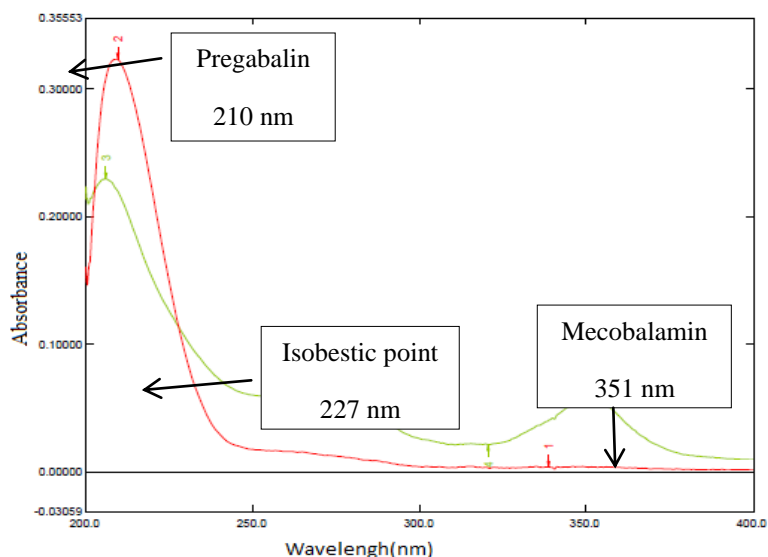

Fig. 3: Overlain spectra of PRG and MCA in 0.1N HCl

The linear range between 15-90 µg/mL for PRG and 0.15-0.9 µg/mL for MCA was observed. Standard calibration curve was plotted between absorbance against concentration of drug shown in Fig. 4 and Fig. 5 for PRG and MCA respectively and the regression equation were calculated. The optical characteristics and other parameter are shown in Table 1.
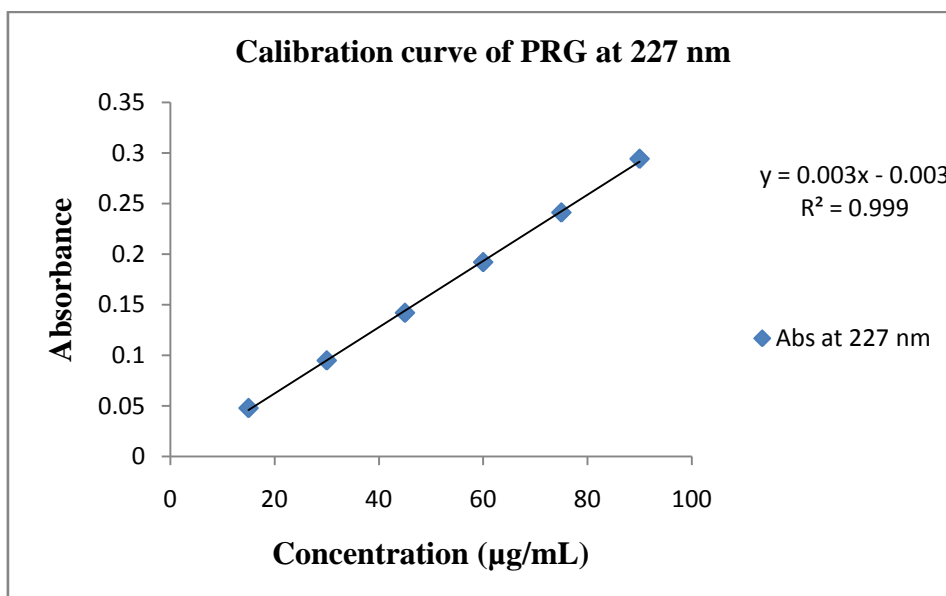
Calibration curve of PRG at 227 nm

y = 0.003x - 0.003
R² = 0.999

◆ Abs at 227 nm

Fig. 4: Calibration curve of PRG

Standard curve for MECO at 351 nm

y = 1.349x - 0.002
R² = 0.999

◆ Abs at 351nm
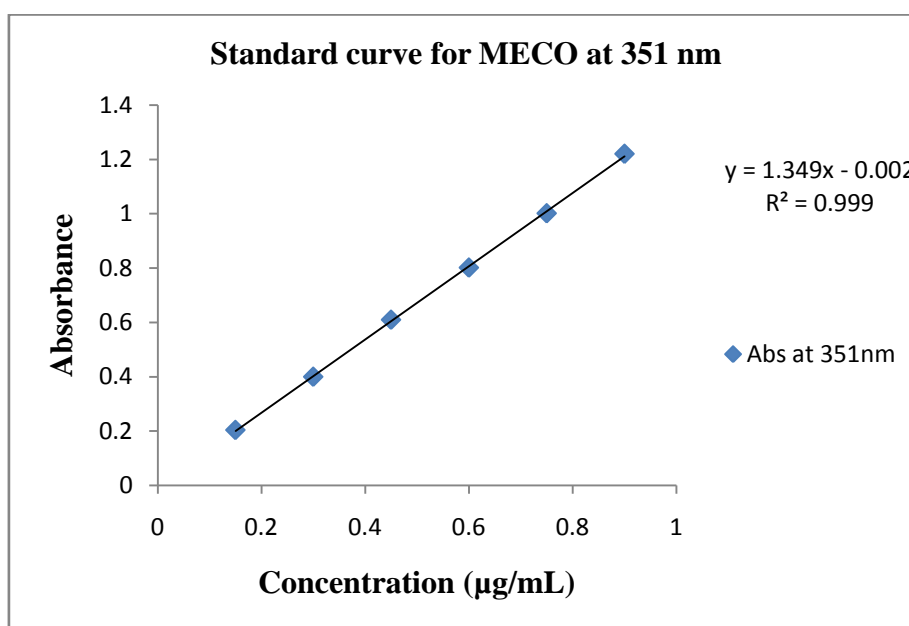
Fig. 5: Calibration curve of MCA

Table 1: Optical characteristics and other parameters

Sr. No.	Parameters	PRG	MCA
1	Wavelength range (nm)	227 nm	351 nm
2	Linearity range (µg/mL)	15-90 µg/mL	0.15-0.9 µg/mL
3	Regression coefficient (r^2)	0.9996	0.9997

4	Slope (m)	0.0033	1.3491
5	Regression equation (y = mx + c)	Y = 0.0033x-0.0031	Y= 1.3491x-0.0028
6	LOD	1.845	0.01662
7	LOQ	6.151	0.05036

The linear relationship was observed between the absorbance and concentration over the range of 15-90 µg/mL and 0.15-0.9 µg/mL for PRG and MCA respectively obeys Beer-Lambert's law with correlation coefficient (r^2) value 0.999 and 0.999 for PRG and MCA respectively. The standard curve was observed for PRG in Fig. 4 and MCA in Fig. 5 respectively. Observations for linearity are tabulated in Table 2.

Table 2: Standard linearity data for PRG and MCA

Sr. No.	PRG		MCA	
	Conc. (µg/mL)	Abs. at 227 nm	Conc. (µg/mL)	Abs. at 351 nm
1	15	0.048	0.15	0.208
2	30	0.095	0.3	0.399
3	45	0.142	0.45	0.609
4	60	0.192	0.6	0.801
5	75	0.241	0.75	1.001
6	90	0.294	0.9	1.220

The accuracy study performs at different addition levels like 80%, 100% and 120%. The mean percentage recovery for PRG was found to be 99.92%, 102.93%, 102.70% and MCA was found to be 99.87%, 100.33%, 101.77% respectively, which are well within the limit and hence the method was found to be accurate. Results for recovery study are shown in Table 3.

Table 3: Result for recovery study

Drug	Levels of % recovery	Amount present (mg)	Amount added (mg)	Amount recovered* (mg)	% Recovery*	S.D.	C.V.
PRG	80 %	75	60	59.95	99.92	1.4747	1.4759
	100 %	75	75	77.2	102.93	0.7490	0.7276

	120 %	75	90	92.44	102.70	0.4356	0.4242
MCA	80 %	0.75	0.6	0.5992	99.87	0.1682	0.1684
	100 %	0.75	0.75	0.7526	100.33	1.3567	1.3522
	120 %	0.75	0.9	0.9133	101.77	1.7267	1.6966

*Average of three determination.

In precision study the % RSD was found to be less than 2, indicate that the given method was precise. The results of precision are shown in Table 4.

Table 4: Result of precision analysis

Parameters	Concentration (µg/mL)		% Estimation*		S.D.		C.V.	
	PRG	MCA	PRG	MCA	PRG	MCA	PRG	MCA
Repeatability	15	0.15	99.25	100.30	0.6963	0.8607	0.7015	0.8781
Interday	15	0.15	102.36	101.46	0.5106	0.8162	0.4989	0.8045
Intraday	15	0.15	102.24	101.86	0.8249	1.5850	0.8069	1.5560

*Average of three determination.

The LOD was 1.845 µg/mL and 0.0166 µg/mL was established for PRG and MCA respectively. The LOQ value was 6.151 µg/mL and 0.0503 µg/mL for PRG and MCA respectively. Results are shown in Table 1.

The % assay was found to be 99.65±0.81 % for PRG and 99.43±0.66 % for MCA in bulk dosage form. The result of % assay is shown in Table 5.

Table 5: Result for analysis of marketed formulation

Sr. No.	Drug	Concentration (µg/mL)	Amount found*	% Label claim*	S.D.	C.V.
1	PRG	15 µg/mL	74.73	99.65	1.0959	1.1019
2	MCA	0.15 µg/mL	0.7457	99.43	0.6638	0.6676

***Average of three determination

The drugs are subjected to various condition like acid hydrolysis, base hydrolysis, neutral hydrolysis, oxidative degradation, photolytic degradation, and thermal degradation. The absorbance for PRG and MCA, after being subjecting to different degradation conditions was compared with the standard. In acid condition the percent degradation was found to be 3% and 4.29% for PRG and MCA respectively. In base condition the percent degradation was found to be 3.44% and 6.8% for PRG and MCA respectively. In neutral condition the percent degradation was found to be 0.77% and 0.49% for PRG and MCA respectively. In oxidative condition the percent degradation was found to be 9.34% and 7.77% for PRG and MCA respectively. In photolytic condition the percent

degradation was found to be 10% and 19.91% for PRG and MCA respectively. In thermal condition the percent degradation was found to be 16.55% and 22.18% for PRG and MCA respectively.

Results of forced degradation data of PRG and MCA are mentioned in Table 6.

Table 6:Result of Forced Degradation study

Sr. No.	Condition	% Degradation		% Assay	
		PRG	MCA	PRG	MCA
1	Acid condition	3	4.29	97.00	95.71
2	Base condition	3.44	6.8	96.56	93.20
3	Neutral condition	0.77	0.49	99.23	99.51
4	Photolytic condition	10	19.91	90.00	80.09
5	Oxidative condition	9.34	7.77	90.66	92.23
6	Thermal condition	16.55	22.18	83.45	77.18

IV. CONCLUSION

The validated stability indicating spectroscopic methods were found to be simple, accurate, precise, rapid, and selective for the simultaneous estimation of PRG and MCA in combined capsule dosage form. The degradation behavior of PRG and MCA was determined by subjecting them in various stress conditions and no attempt was made to identify the degradation product.

V. ACKNOWLEDGEMENT

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