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Spectrofluorimetric Determination of Some N. Containing Medicines Using Rhodamine 6G as a Chromogenic Reagent

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Abstract

A sensitive spectrofluorimetric method has been developed for the analysis of some medicines containing primary, secondary, and tertiary amino groups, namely Diclofenac (DIC), Domperidone (DOM), Famotidine (FAM), and Propranolol (PRO), in their pure and medicinal forms. The method is based on the quenching of the fluorescence intensity of rhodamine 6G (R-6G) through the formation of ion-pair complexes between the above medicines and the R-6G reagent, which is measured at 552 nm after excitation at 402 nm. The calibration graphs were rectilinear in the concentration ranges of 0.10- 9.00, 0.05-15.00, 0.10-14.0 and 0.05-5.00 µg mL^{-1} for above medicines respectively. The recovery (%) values were ranged between 99.45%-100.97%. The detection limits ranged in the concentration of 0.243-0.754 µg/mL, and the limits of quantitation were 0.806- 2.420 µgmL^{-1} for all drugs. The method was successfully applied for the determination of these drugs in their pharmaceutical preparations.

Keywords: Amino medicines, Rhodamine 6G, Ion-pair complexes, Spectrofluorimetry

Introduction

Nitrogen is a constituent of every major pharmacological drug class, approximately 42% of drugs and drug candidates contain amine functional groups [1], such as antibiotics, nonsteroidal anti-inflammatory, antiemetic, H_2 receptor antagonist, beta adrenoceptor drugs, and others.

DIC, chemically named as 2-[(2,6-dichlorophenyl)aminophenyl]acetate (I), which decreases inflammation and pain, is a drug. It is a nonsteroidal anti-inflammatory drug used to treat pains and aches, as well as joint, muscle, and bone disorders. These involve osteoarthritis, rheumatoid arthritis, gout sprains, ligaments, muscle strains, back pain, spondylitis that causes inflammation of the spine, toothaches, and migraines, and other sections of the body [2,3].

DOM malate, chemically named as 5-Chloro-1-(1-[3-(2-oxo-2,3-dihydro-1*H*-benzo [*d*]imidazol- 1-yl)propyl]piperidin–4-yl)-1*H*-benzo[*d*]imidazol-2(3*H*)-one (II) is also called Motilium [4]. It is an antiemetic drug used as an "anti-vomiting" drug for vomiting and nausea caused by diseases of the digestive tract, especially those that appear as side effects of other drug treatments, especially anti-cancer drugs or radiation therapy [5], and it is also used for anti-dopamine treatments for Parkinson's disease [6]. FAM, chemically named as 3-[({2-[(diaminomethylidene)amino]-1,3 – thiazol - 4 -yl}methyl)sulfanyl] – *N* -sulfamoylpropanim-idamid (III) is one of the medicines used to treat peptic ulcers, as it is considered a type II antihistamine (H_2-receptor blockers) that inhibits the excessive secretion of stomach

acid, eliminating heartburn especially in the stomach and esophagus, and speeding up the healing of ulcers [7-9]. PRO, chemically named as (*RS*)-1-(1-methylethylamino)-3-(1-naphthyloxy)propan-2-ol (IV) known since 1965, was the first beta-blocker in common use (Fig.1). PRO is beta adrenoceptor drug used to treat hypertension, angina pectoris, and arrhythmia. This drug is also effective in returning a fast heartbeat to its balanced rate and other symptoms caused by hyperthyroidism (Hyperthyroidism) and reducing heart rate, sweating, and trembling caused by severe anxiety. PRO is also used to prevent migraine attacks [10].

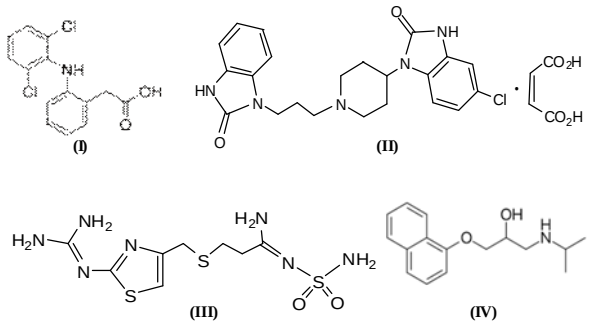

Figure 1. **Structure of DIC (I), DOM (II), FAM (III) and PRO (IV)**

Several analytical techniques have been described for the determination of the above drugs in their pure form and pharmaceutical formulations. These include HPLC [11-18], spectrophotometric [19-28], conductometric [29], and electrochemical methods [30-33] were described for the determination of these drugs. Few spectrofluorimetric methods have been reported in the literature for the determination of the studied drugs. These methods are either direct determination, depending on the measurement of the fluorescence intensity of the ion-pair complexes, or indirect determination by measurement of the quenching fluorescence of the dye through the formation of ion-pair complexes with these drugs, such as 7-fluoro-4-nitrobenzo-2-oxa-1,3-diazole (NBD-Cl) [34], α-cyclodextrin [35] for DIC, 9, 10-phenanthraquinone [36] for FAM and eosin Y [37] for PRO. R-6G is one of the most widely used dyes in dye laser and fluorescence tracer. Aqueous R-6G solutions are interesting when the dye is used as a fluorescence tracer [38]. It was used for indirect determination of some medicines depending on the addition of an excess amount of oxidizing agent and the unreacted oxidizing agent such as N-bromosuccinimide, ceric sulphate [39,40], and bromate bromide [41] that are decreased the signal of R-6G, which are directly proportional to the concentration of medicines. However, some of these methods suffer from one or more disadvantages such as expensive instrumentation, time-consuming, tedious extraction procedures, and low sensitivity. The present paper reports a simple spectrofluorimetric determination of some N-containing drugs based on their quenching the fluorescent intensity of rhodamine 6G dye.

Materials and Methods

Instrumentation

RF-5301 PC- Spectrofluorophotometer equipped with xenon lamp and 1 cm quartz cell was used. Philips PW 94 instrument supplied with CE 10-12 pH electrode was used for pH measurements. An electronic balance of D0001.A&D Company Limited model was used for weighing.

Chemical and Reagents

All reagents and solvents were of analytical reagent grade provided by Fluka and BDH companies. R-6G was prepared in a concentration of 50 μgmL^{-1} by dissolving 0.01 g in distilled water, and the volume was completed to 200 mL with distilled water in a volumetric flask. Acetate buffer solution (pH3.5) was prepared by dissolving 16.02 g of

sodium acetate in 300 mL of distilled water. Then the pH was adjusted with acetic acid to 3.5 and complete the volume to 1 L with distilled water. Phthalate Buffer solution (pH6) was prepared by mixing 50 mL of 0.2 M potassium hydrogen phthalate with 45.4 mL of 0.2 M sodium hydroxide, and volume completed to 200 mL with distilled water in a volumetric flask. The pH values were adjusted by the pH meter.

DIC and PRO were prepared in a concentration of 100 μgmL^{-1} by dissolving 0.01 g of each drug in distilled water and complete the volume to 100 mL in a volumetric flask with distilled water. DOM and FAM were prepared in a concentration of 100 μgmL^{-1} by dissolving 0.01 g of each drug in wormed distilled water with mixing, then cooled and completed the volume to 100 mL in a volumetric flask with distilled water. All the solutions were kept in the refrigerator.

Procedure

Aliquots of working stock solutions containing DIC, DOM, FAM, and PRO were added separately into 10 mL volumetric flasks containing 20 μgmL^{-1} R-6G in addition to 1.5 mL acetate buffer solution of pH3.5 for DIC, FAM, and 2 mL for PRO and containing 2 mL of phthalate buffer solution of pH 6 for DOM. The volumes were completed to the mark with distilled water, and the fluorescence intensity of solutions was measured at λem 552 nm after excitation at λex 402 nm against a blank solution. The fluorescence intensity (ΔF) was plotted against the concentration of drugs in the final volume.

Analysis of Pharmaceuticals
DIC sodium, PRO, DOM and FAM tablets

From each pharmaceutical form, 10 tablets of Voltaren (containing 100 mg DIC sodium), 7 tablets of Inderal (containing 40 mg PRO), 10 tablets of Dompy (containing 10 mg DOM malate), and 10 tablets of Gastrofam (containing 40 mg FAM). Each sample was ground and mixed well.Then accurately weighed equivalent to one tablet for each formulation which was dissolved in a few drops of ethanol to increase the solubility and completed with distilled water. The solutions were filtered through a Whatman no. 42 filter paper and completed to the suitable volumes with distilled water in volumetric flasks separately. Aliquots of each solution containing the amount within the corresponding calibration curve were analyzed as cited in the recommended procedure.

DIC sodium ampule

Three pharmaceutical ampoules (Voltaren), each one contain 75 mg/ 3 mL DIC sodium, were mixed well, then 1.0 mL volume of content was diluted to 100 mL with distilled water to obtain 250 μgmL^{-1}. This solution was further diluted, and the concentration of the drug per ampoule was determined using its respective calibration graph constructed for pure form by following the recommended procedure.

Results and Discussion

Methods for estimating the fluorescence of ion-pair complexes generally depend on the quenching process. In ion-pair, if one of the ions is a fluorophore, the counter ion behaves as a quenching agent. With a certain concentration range, the fluorescence decreases in proportion to the analyte concentration [42]. This study aims to develop a sensitive spectrofluorimetric method for the assay of DIC, PRO, FAM, and DOM drugs in their pure forms and dosage forms. In this study, it was found that R-6G dye has fluorescent emission at 552 nm after excitation at 402 nm (Fig. 2). When the above drugs are added to the dye, a significant

quenching of fluorescence intensity has been observed, and increased in an acidic medium has occurred. This may be due to the formation of non-fluorescent ion-pair complexes by electrostatic attraction between medicines and the dye [37,43-45]. The decrease of fluorescence intensity of R-6G is found to be a linear function of N-containing medicines concentrations in water solution.

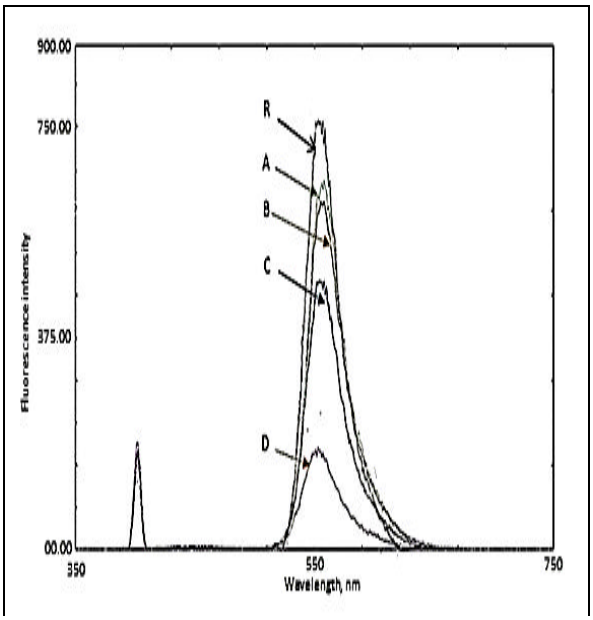

Figure 2. **Effect of (A) 1µgmL^{-1} PRO, (B) 3 µgmL^{-1} DIC, (C) 14 µgmL^{-1} FAM and (D) 15.5 µgmL^{-1} DOM on the quenching of ® 20 µgmL^{-1} R-6G dye**

However, the method is dependent on the measurement of the quenching of fluorescein dye which is proportional to the concentration of studied medicines.

Optimization of Conditions

Various experimental factors affecting the fluorescence intensity of the complexes have been studied and optimized, such factors were changed individually while others were kept constant. These factors include a selection of R-6G dye concentration, pH, buffer solution, temperature, and solvent.

Selection of R-6G Concentration

To select the optimum concentration of R-6G dye for the determination of the intended medicines, a calibration graph was constructed by plotting absorbance versus aliquots of 50 µgmL^{-1} of dye in a set of 10 mL calibrated flasks and diluted to the mark with distilled water. The emission of fluorescence intensity was measured after 10 min at 552 nm after excitation at 402 nm.

The linearity was found in the range of 0.1-20.0 µgmL^{-1} (Fig. 3). However, 20 µgmL^{-1} of R-6G dye was selected for analysis of the drugs in this study.

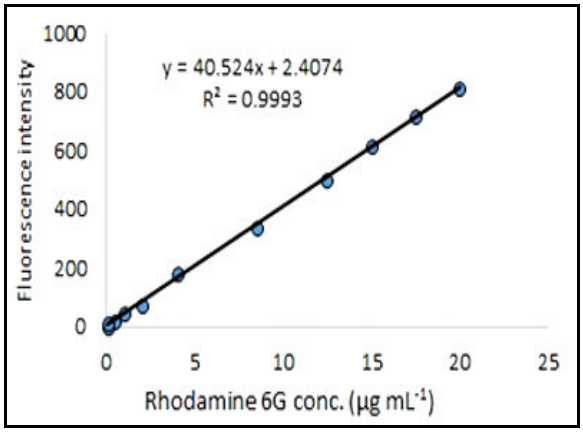

Figure 3. **Calibration Graph of R-6G day**

Effect of pH and Buffers

The effect of changing pH on the fluorescence intensity for the complexes was studied by the addition of different buffer types with different pHs such as acetate, phthalate, and citrate of pH ranges 3-6 were prepared and examined. As seen in Table 1, acetate buffer of pH 3.25 gave maximum ΔF for DIC, PRO and FAM drugs, whereas phthalate buffer of pH 6 for DOM drug, with volumes of 2, 1.5, 1.5, and 2 mL, respectively (Table 2), which are chosen as the optimum throughout the study.

Table 1. **Effect of pH on the intensity (ΔF) of drugs.**

Type of buffer solution	pH	ΔF			
		PRO	FAM	DOM	DIC
Acetate buffer	3.0	121	49	37	220
	3.25	125	52	42	222
	3.5	122	53	38	199
	4.0	120	56	38	170
	4.5	115	56	32	171
	5.0	110	58	30	175
	5.25	90	59	27	175
	5.5	85	64	27	180
	6.0	77	73	22	174
Phthalate buffer	3.0	121	50	35	212
	3.25	121	52	35	218
	3.5	121	55	33	216
	4.0	117	57	30	200
	4.5	107	60	28	180
	5.0	100	60	27	188
	5.25	100	61	27	189
	5.5	87	69	25	189
	6.0	80	75	22	187
Citrate buffer	3.0	110	40	33	200
	3.25	112	40	39	190
	3.5	100	39	35	187
	4.0	99	40	35	178
	4.5	99	49	33	175
	5.0	99	49	30	166
	5.25	92	54	32	162
	5.5	87	57	28	162
	6.0	80	69	28	160

Table 2. **Effect of buffer solution volume on the intensity (ΔF) of drugs.**

Buffer	Volume (mL)	ΔF			Buffer solution	ΔF
		DIC	FAM	PRO		DOM
Acetate buffer	0.25	111	30	220	Acetate buffer	61
	0.50	115	33	222		64
	0.75	120	37	199		70
	1.00	125	42	222		75
	1.25	129	46	130		79
	1.50	134	50	240		83
	1.75	137	50	240		87
	2.00	140	50	237		90
	2.25	138	50	237		90
	2.50	138	50	237		89

Effect of temperature and time

The temperature effect ranging from 28°C (R.T) to 40°C and time on the quenching the fluorescence intensity of R-6G for the studied medicines, in the presence of suitable buffer solution, were studied. It was found that the fluorescence intensity (ΔF) was increased after 5 min at room temperature and remained stable for more than 200 min (Fig. 4). Whereas decreasing in intensity was found at 40°C. However, a standing time of 5 min was chosen for all drugs.

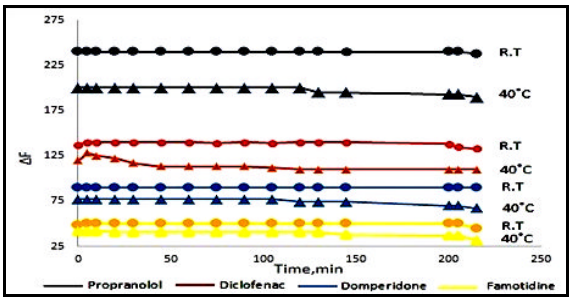

Figure 4. **Effect of the temperature and the developing time on the intensity (ΔF) of medicines**

Effect of diluting solvents

Dilution effects with water and other different organic solvents, such as acetone, methanol, ethanol, dimethylformamide (DMF), and dimethyl sulphoxide (DMSO), were examined on the fluorescence intensity. The results indicated that water was the best solvent, whereas the organic solvents decreased the fluorescence of R-6G dye (Fig. 5). Therefore, water was recommended as a diluting solvent.

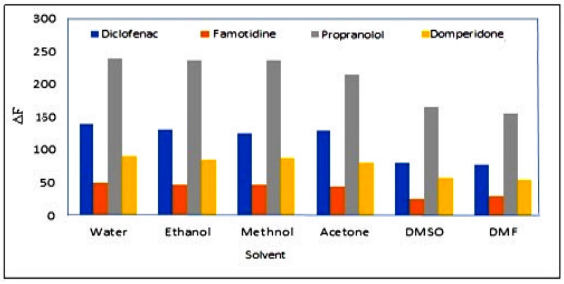

Figure 5. **Effect of solvents on the intensity (ΔF) of drugs**

Effect of surfactants

Different surfactants such as triton x-100 (Tr-100), tween 80 (Tw-80), sodium dodecyl sulphate (SDS), and cetylpyridinium chloride (CPC) were examined. As shown in Fig. 6, The results indicated decreased fluorescence intensity (ΔF). Therefore the surfactants were omitted in this study.

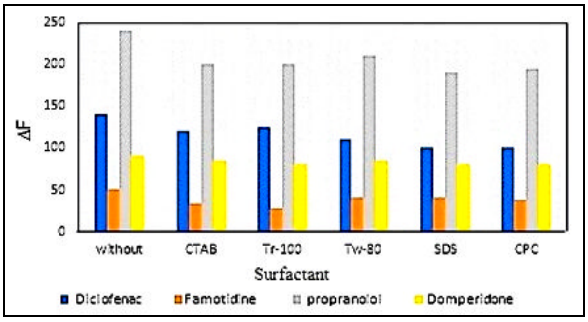

Figure 6. **Effect of surfactant on the fluorescence intensity (ΔF) of drugs**

Effect of sequence addition

Four sets of drug solutions were prepared but with a different order of additions. Under the previous optimum conditions, the sample solutions were measured at λex= 402 nm and λem=552 nm for DIC, DOM, FAM, and PRO against their corresponding blank solution, respectively. As demonstrated in Figure 7 show that the addition of R-6G followed by buffer solution and the drug was gave maximum intensity (ΔF) and recommended in the general procedure.

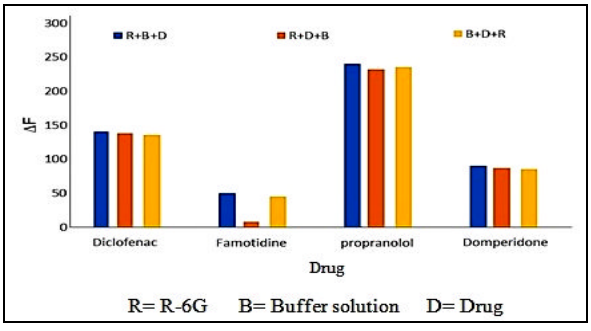

Figure 7. **Effect of a sequence of additions**

Effect of pharmaceutical excipients

The effect of common excipients used in pharmaceutical formulations such as starch, glucose, lactose, sucrose and sodium chloride, Mg-stearate, sodium sulphate, and potassium chloride were investigated for all studied drugs. The results cited in Table 3 indicated no interference could be observed within a 200 fold excess of excipient present in the proposed method.

Table 3. **Effect of excipients on the recovery % of drugs.**

Excipient	Recovery % of 2.5 μgmL^{-1}							
	DIC		DOM		FAM		PRO	
	500	100	500	100	500	100	500	100
Starch	99.21	94.54	97.54	95.01	95.92	95.54	95.43	95.69
Glucose	98.89	96.10	98.25	96.22	98.97	95.90	98.44	97.41
Lactose	100.50	96.95	99.10	94.95	97.92	97.20	96.17	95.98
Sucrose	98.94	97.58	97.99	95.57	97.72	97.24	95.44	96.31
KCl	99.32	95.02	98.00	95.36	98.99	94.25	98.54	97.00
NaCl	100.95	95.23	96.95	96.11	100.89	97.39	99.99	97.01
Na_2SO_4	99.01	95.23	99.00	97.58	95.00	95.02	95.85	95.05
Mg-stearate	99.01	95.32	99.23	95.65	99.21	97.32	99.91	95.37

Calibration graphs and analytical results

Calibration graphs were plotted under the optimum experimental conditions constructed to the difference in fluorescence intensity (ΔF) as a function of the corresponding DIC, PRO, FAM, and DOM concentrations in μg mL^{-1}, where calibration graphs showed excellent linearity in the ranges 0.1-9.0, 0.05-5.0, 0.1-14.0 and 0.05-15 μg mL^{-1} for above medicines, respectively (Fig. 8). The characteristics of the calibration graphs are summarized in (Table 4).

***Table 4*. The characteristics of the calibration graphs.**

Parameters	PRO	DIC	DOM	FAM
Linearity range ($\mu g mL^{-1}$)	0.05-5.0	0.1-9.0	0.05-15	0.1-14.0
Slope	120.81	68.458	40.154	24.209
Intercept	3.895	0.3213	4.6381	1.8015
R^2	0.9991	0.9996	0.9992	0.9994

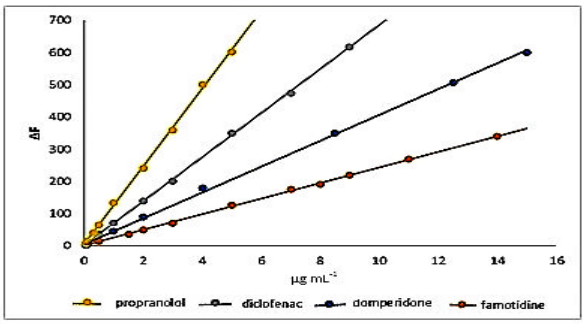

***Figure 8*. Calibration graphs for the studied drugs**

Accuracy and precision

The accuracy was examined using three replicate analysis for each of three different concentrations within the calibration graph of each drug. The results, cited in Table 5, show the agreement between the true and measured values indicating good accuracy of the suggested method. The relative standard deviation (RSD) values were calculated and found to be ≤ 2.56 for all the studied drugs indicating good reliability and repeatability of the method.

***Table 5*. Accuracy and precision of the method.**

Drug	Amount added ($\mu g mL^{-1}$)	Recovery* %	Average recovery %	RSD
DIC	2	104.21	100.97	1.19
	5	100.70		2.33
	7	98.01		0.79
DOM	3	100.33	100.25	0.73
	6	100.18		2.56
	9	100.26		1.98
FAM	3	96.65	99.45	1.02
	6	100.65		0.57
	9	101.06		1.32
PRO	1.5	100.49	99.48	1.1
	3	97.70		1.0
	4.5	100.26		1.2

*Average of five determinations

Method validation

To check the validity of the proposed method, it was applied successfully for the determination of DIC, DOM, FAM, and PRO in their commercial dosage forms as injection and tablets. The obtained values of recovery % are cited in Table 6 which indicate good accuracy and showed no serious interferences with the excipients. The results obtained by the suggested method were statistically compared with those of official methods [46], which are dependent on potentiometric titrations for their pure forms. By applying t-test for accuracy and F-test for precision at 95% confidence level with four degrees of freedom. The experimental values for t and F tests, as seen in Table 6, did not exceed the theoretical values (t =2.78, F = 6.39). This confirmed that there are no significant differences between the proposed method with the official method.

***Table 6*. Determination of DIC, DOM, FAM and PRO in their dosage forms by the proposed method.**

Pharmaceutical preparations	Recovery [a] (%)			
	Present method	Standard method[37]	$t_{exp.}$	F_{test}
Voltaren injection	98.37	99.41	1.20	1.62
Dompy tablet	100.09	99.71	1.21	1.51
Gastrofam tablet	99.21	98.17	1.73	1.47
Inderal tablet	98.74	99.25	0.98	1.01

Conclusion

A new simple, accurate and sensitive spectrofluorimetric method has been proposed for the determination of DIC, DOM, FAM, and PRO drugs in bulk and their dosage forms. The method is dependent on the measurement of the quenching fluorescence intensity of R-6G dye through the formation of ion-pair complexes between the studied drugs and the dye. The proposed method is free from interference by common additives and excipients and does not require any pretreatment or extraction steps.

Conflict of Interest

The authors declare that there is no conflict of interest.

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