CHROM. 4332

DETERMINATION OF HYDANTOINS IN PHARMACEUTICAL PREPARATIONS BY GAS CHROMATOGRAPHY

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(First received May 13th, 1969; revised manuscript received August 8th, 1969)

SUMMARY

The gas chromatographic method described is considered a quick routine analytical control method both for the assay of pure hydantoins and of those in drug form.

INTRODUCTION

Hydantoins are cyclic ureides related in structure to barbiturates. The hydantoins, *e.g.* Diphedan (5,5-diphenylhydantoin) and Sacerno (5-ethyl-3-methyl-5-phenylhydantoin), are anticonvulsants most effective against "grand mal" and psychomotor seizures[1,2]. Diphedan and Sacerno are chosen for this investigation because they are good representative examples of the hydantoins and because they are available, have a wide application and acceptance and are most commonly used in pharmacy and medicine.

The official method of assaying the hydantoins is through the determination of their nitrogen content, based on the principle of the Kjeldahl method. The disadvantage of this method is that it does not differentiate between hydantoins and that it determines only the total nitrogen content. In addition, this long, tedious method has a wide range of error. The added ingredients, usually prescribed with the active constituent, may interfere with the method leading to inaccurate results. Also this assay is not applicable in the presence of biological fluids.

From the above discussion, it is evident that an improved accurate analytical method for the determination of hydantoins, especially those in drug form, is needed.

Gas chromatography is considered a desirable technique and has been found very suitable for analysis. Few such methods have been reported in the literature[3–5].

The purpose of this study was to develop a rapid specific gas chromatographic procedure for hydantoins. Such a method would not be subject to the limitations of the official method and would be suitable for determining and assaying samples both in pure and in drug form.

EXPERIMENTAL

A Carlo Erba Fractovap, Model D, gas chromatographic apparatus with a Carlo Erba integrator, Model 75, equipped with a flame ionization detector and a Kienzle-type printer were used. The optimum values of gas chromatographic parameters found are shown in Table I.

TABLE I

THE OPTIMUM VALUES OF GAS CHROMATOGRAPHIC PARAMETERS

Detector:	FID
Attenuation:	64 × 100 for dioxan and Sacerno 8 × 100 for Diphedan
Carrier gas:	nitrogen
Carrier gas inlet pressure:	1.65 kp/cm²
Carrier gas flow rate:	6.52 ml/min, measured at 765 torr and 22.8°
Auxiliary gases:	oxygen, inlet pressure: 1.75 kp/cm² hydrogen, inlet pressure: 1.25 kp/cm²
Column:	spiral of stainless steel, 3.0 m × 4.0 mm I.D.; packing: 12.5 w/w % SE-30 on 60/80 mesh Chromosorb W
Column temperature:	256.0 ± 0.1 °
Temperature of the evaporator:	369.0 ± 1.0 °
Recorder:	Speedomax G; 2.5 mV; 1 sec
Paper speed:	1.27 cm/min

Fig. 1 shows the typical chromatogram, under optimum conditions for analysis, of Diphedan and Sacerno.

The pure active constituents, Diphedan and Sacerno, were first quantitatively analyzed, using 1–5 w/w% solutions in dioxan. Certain known aliquots were taken for analysis. Fig. 2 shows the calibration curve of the pure active constituents, with the corrected integrator values. Values were corrected from the integrator-measured area,

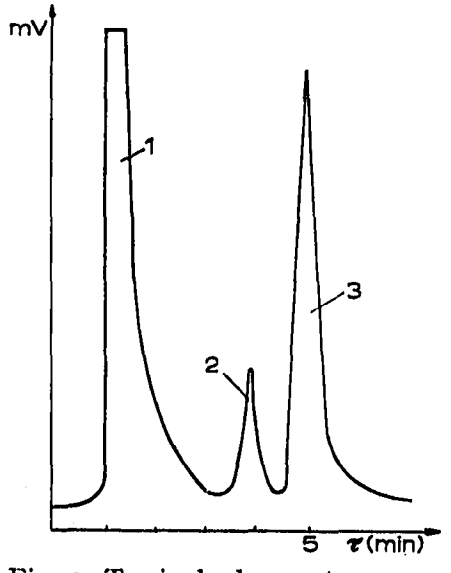


Fig. 1. Typical chromatogram, under optimum conditions for analysis, of Diphedan (2) and Sacerno (3). The first peak on the chromatogram represents dioxan.

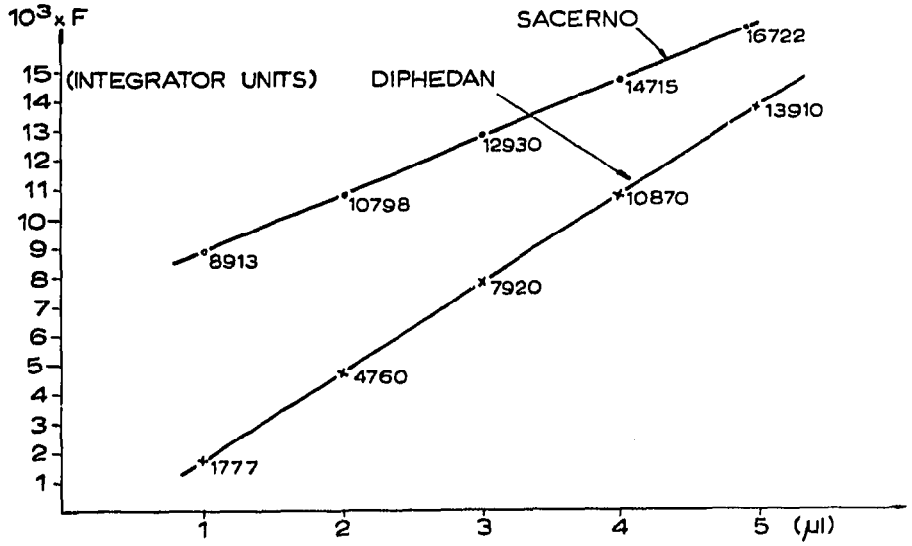


Fig. 2. Calibration curves of the pure active constituents.

while in practice there was always a difference between the base line of the apparatus and the work line of the integrator.

Consecutively, Diphedan and Sacerno in drug form were quantitatively analyzed. The tablets were prepared for analysis by the usual standard pharmacopoeia methods, using dioxan as the solvent. A solution of 1–10 w/w% of each was prepared. Certain known aliquots were taken for analysis. The peak areas were measured with the Carlo Erba integrator, Model 75.

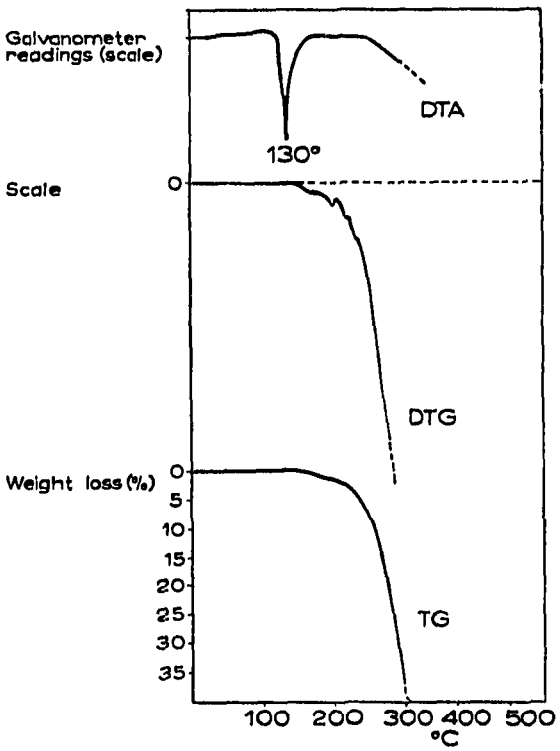
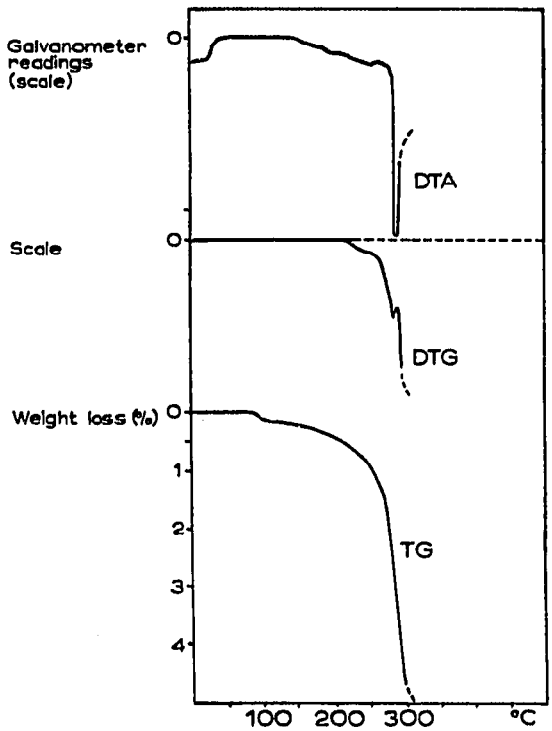


Fig. 3. Derivatogram of Sacerno.



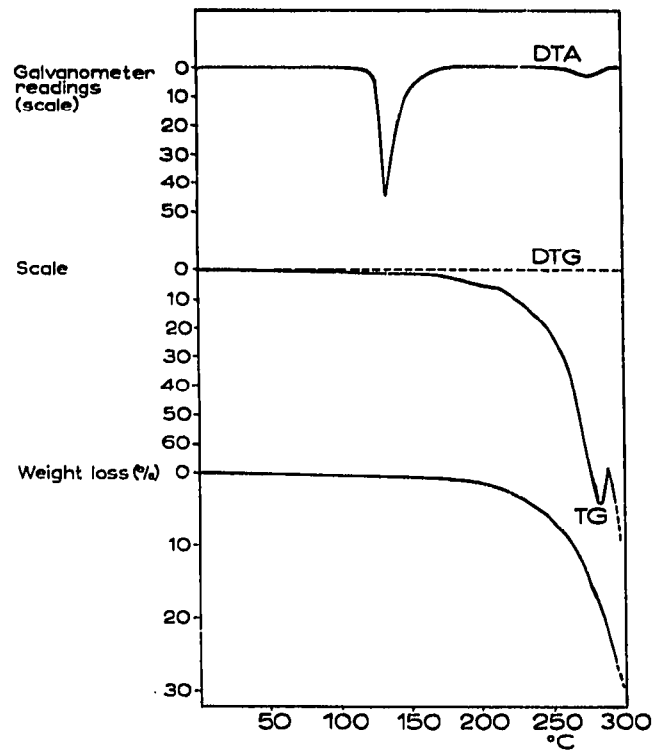


Fig. 4. Derivatogram of Diphedan.

Fig. 5. Derivatogram of the Sacerno–Diphedan (1:1, w/w) mixture.

This corrected improved method was then applied for the final quantitative determination of Diphedan and Sacerno, as pure active constituents as well as in drug form.

For completing the gas chromatographic examinations, derivatograms of Diphedan and Sacerno were made using a Derivatograph instrument (MOM, Budapest, Hungary)[6,7]. The derivatograms are shown in Figs. 3–5.

Fig. 3 shows that up to 150° Sacerno contains neither volatile components nor, in addition, any adsorbed moisture (DTG and TG curves). The DTA curve shows that Sacerno melts at 130° (endothermic peak maximum); above this temperature, at 150°, decomposition takes place in the melted phase and, up to 300°, about 40 w/w% of the sample decomposes.

Fig. 4 shows that Diphedan is practically thermostable up to 100°. Above 100° a slow decomposition process begins, reaching its maximum speed at 290°.

Fig. 5 shows the DTA curve at 130° with the endothermic peak maximum, characteristic for Sacerno. The maximum which appears at 290° on the DTG curve indicates the maximum decomposition speed of Diphedan. An evaluation of the derivatogram of the mixture proved that Sacerno melts at 130° and that, in its melted phase, Diphedan is slowly dissolved. Thus, the viscosity of the melted phase becomes greater, and the loss in weight becomes smaller in relation to what was mentioned before.

Finally we should point out that there is a possible contradiction between the temperature used in gas chromatography and the one used in derivatography. The

reason for this contradiction is that the materials decompose at a lower temperature in derivatography than at the temperature used in gas chromatography. The conditions of the two procedures have been quite different. For derivatographic analysis, the work is carried out in a static air atmosphere in the presence of oxygen, which is contrary to the conditions for gas chromatography, where a dynamic nitrogen atmosphere exists in the absence of oxygen. Under the latter conditions, dioxan also does not decompose[8]. This phenomenon had already been observed[8], but an exact explanation could not be given.

ACKNOWLEDGEMENT

The authors are grateful to the United Works of Pharmaceutical and Dietetic Products (Budapest, Hungary) for their generous supply of pure hydantoins and tablets.

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