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THERMAL ANALYSIS OF PHARMACEUTICAL COMPOUNDS

III. CHARACTERIZATION OF SULPHONAMIDES BY THERMAL ANALYSIS

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Fourteen sulphonamides have been thermally analyzed using thermogravimetry (TG), derivative thermogravimetry (DTG) and differential thermal analysis (DTA). Their thermal reactions and stabilities have been thoroughly studied. It was found that the sulphonamides are first transformed into sulphanilamide. The melting points of these sulphonamides have been determined through their DTA curves and by the Kofler microscope, the results agreeing with those reported in the literature. The amount of water of crystallization has been calculated from the TG and DTG curves. Analysis of mixtures of some sulphonamides has been achieved by thermal analysis and by thin-layer chromatography using different solvent systems.

Thermal analysis has been used for the analysis of diverse compounds such as carbohydrates [1, 2], sweetening agents [3], herbicides [4], pig's fat [5], furocoumarins and others [6, 7].

Sulphonamides are a popular group of chemicals used in medication. Hundreds of procedures are known for their detection and determination [8]. The use of thermal analysis for sulphonamides has so far been very limited [9, 10].

A series of thermal analyses of pharmaceutical compounds was earlier started by this group with the thermal analysis of antibiotics [11] and antihistaminics [12]. As a continuation, the thermal analysis of sulphonamides is now reported. Fourteen sulphonamides have been thermally analyzed by TG, DTG and DTA. The aim was to identify and compare their thermal behaviours, decomposition pathways and thermal stabilities. Mixtures of sulphonamides have also been examined by thermal analysis and TLC.

Experimental

Procedure: 0.1 g of each sulphonamide (or mixtures of equal amounts) was accurately weighed in a platinum crucible and treated in a derivatograph (MOM, Budapest, Hungary) under the following conditions: sensitivity of balance 100 mg, sensitivity of DTG and DTA galvanometers 1/10 (in the case of mixtures it was 1/3 for the DTA galvanometer), heating rate 5°/min, recording time 100 min;

the temperature was raised linearly from room temperature (20–25°) to 50; the reference material used was Al_2O_3 (May & Baker) previously heated to 1200° for one hour.

Results and discussion

The chart obtained from the apparatus (which is graduated for temperature and weight loss measurements) for a single compound includes temperature or heating rate (T), DTA, TG and DTG curves. The temperatures of the start and end of the reactions were obtained with the aid of T, TG and DTG curves (it is easier and more correct to trace the beginning and ending of the DTG peaks than from the TG curve, which may be steep). The same discussion holds for the percentage weight loss, which was obtained from the DTG and TG curves together, since the TG curve alone does not clearly show the end of the reaction.

The purities of the sulphonamides were determined by a pharmacopoeial method [14, 15] and all the results obtained have been appropriately corrected. The non-significant figures for the percentage weight loss have been excluded.

As an example, the complete chart for sulphacetamide sodium, including the necessary enumerations, is presented in Fig. 1.

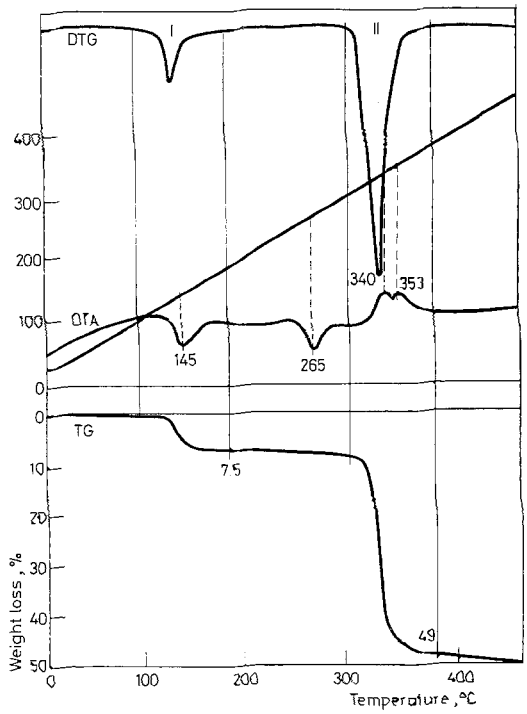

Fig. 1. TG, DTG and DTA curves of sulphacetamide sodium

To save space, collective figures are drawn together, in which the DTA, DTG and TG curves (Figs 2–4) of the 14 sulphonamides (as examined singly), obtained from their original charts, are presented. Table 1 illustrates the different thermal reactions of the sulphonamides, which differ in their number according to the examined member.

In the cases of sulphacetamide sodium, sulphaguanidine and succinyl sulphathiazole, the first endothermic peak in the DTA curve and the first reaction in the DTG curve are due to the loss of water of crystallization.

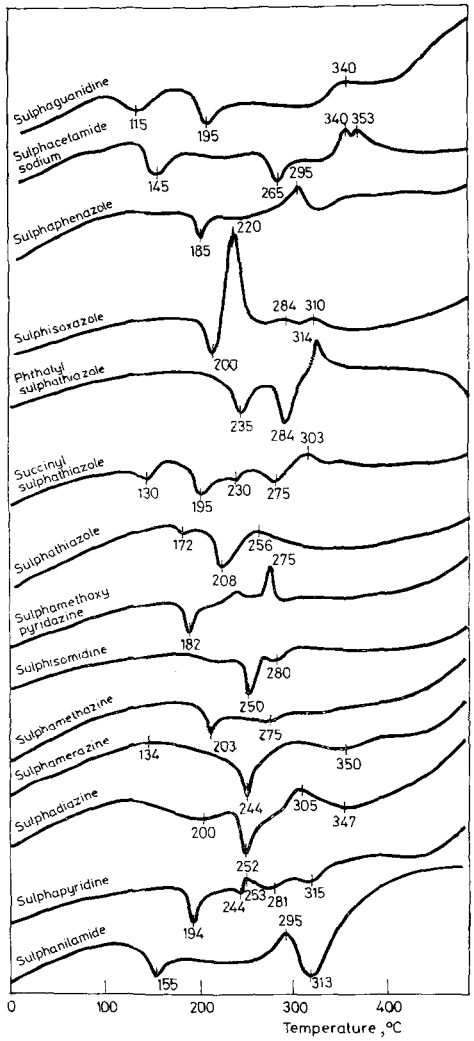

Fig. 2. DTA curves of sulphonamides

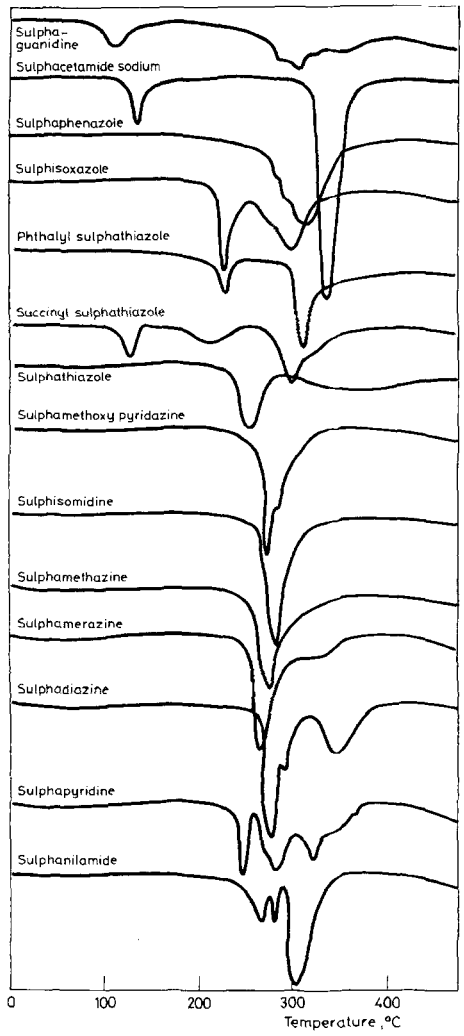

Fig. 3. DTG curves of sulphonamides

The thermal stabilities of the sulphonamides increase in the order succinyl sulphathiazole < phthalyl sulphathiazole < sulphisoxazole < sulphaguanidine < sulphaphenazole < sulphapyridine < sulphamethoxypyridazine < sulphadiazine < sulphanilamide and sulphisomidine. In most cases this agrees with the results of Schittenhelm *et al.* [13].

Table 2 shows the temperatures of the endothermic and exothermic peaks, together with the melting points determined by Kofler microscope (Reichert,

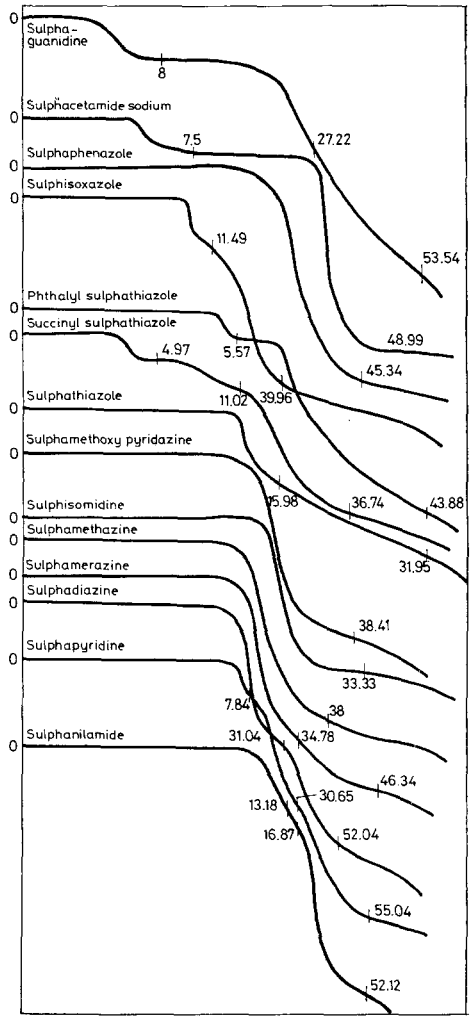

Fig. 4. TG curves of sulphonamides

Austria) and those stated in the literature [14, 15]. It is noticed that the first endothermic peak is in accordance with the melting points of the examined sulphonamides determined by Kofler microscope and those from the literature. In the case of sulphathiazole, two endothermic peaks are obtained in the DTA curves which are not accompanied by weight loss; this may be due to the presence of two polymorphic forms with different melting points.

Table 1

Different reactions of sulphonamides when thermally treated

Sulphonamides	First reaction			Second reaction				Third reaction			
	start, °C	end, °C	weight, loss %	start, °C	end, °C	weight loss, %		start, °C	end, °C	weight loss, %	
						total	specific			total	specific
Sulphanilamide	244	282	13.2	282	298	16.9	3.7	298	360	52.1	35.2
Sulphapyridine	228	254	7.9	254	302	30.7	22.8	302	392	55	24.3
Sulphadiazine	240	312	31	312	377	52	21				
Sulphamerazine	235	312	34.8	312	391	46.3	11.5				
Sulphamethazine	234	350	38								
Sulphisomidine	255	373	33.3								
Sulphamethoxypyridazine	237	370	38.4								
Sulphathiazole	232	290	16	290	440	32	16				
Succinyl sulphathiazole	100	144	5	186	260	11	6	260	383	36.7	25.7
Phthalyl sulphathiazole	200	243	5.6	255	450	43.9	38.3				
Sulphisoxazole	202	240	11.5	240	325	40	28.5				
Sulphaphenazole	285	372	45.3								
Sulphacetamide sodium	98	186	7.5	310	378	49	41.5				
Sulphaguanidine	76	154	8	220	318	27.2	19.2	318	424	53.5	26.3

* Specific weight loss is the weight loss occurring only in the given reaction (second or third reaction) and not including the weight loss due to the preceding reaction(s) (cf. total weight loss).

Decomposition pathway of sulphonamides

During heat treatment, it is possible that sulphonamides are first transformed to sulphanilamide (which is more stable). The weight losses equivalent to the transformation of sulphonamides to sulphanilamide as theoretically calculated are found to be in agreement with the total weight losses obtained from the DTG and TG curves at the end of the second decomposition reaction for sulphapyridine, sulphisoxazole and sulphathiazole, and at the end of the first decomposition reaction for sulphadiazine, sulphamethoxypyridazine, sulphisomidine, sulphaphenazole, sulphaguanidine, sulphamerazine and sulphamethazine. This assumption is further confirmed practically by examining the residue remaining during and at the end of the reactions of interest for sulphanilamide and the intact compound. This is achieved by TLC, using reference compounds: 0.5% solution of each of the examined sulphonamides in 0.1 *N* sodium hydroxide; developing system: *n*-butanol : water (10 : 1) [16]; adsorbent: alumina containing 15%

Table 2

Temperatures of endothermic and exothermic peaks of sulphonamides when thermally treated, together with their melting points

Sulphonamides	M. P. (Literature) °C	M. P. (Kofler microscope) °C	Temp. of endothermic peaks, °C	Temp. of exothermic peaks, °C
Sulphapyridine	191–193	191–194	*194*, 244, 281, 315	253
Sulphadiazine	252–256	247–250	200, *252*, 347	305
Sulphamerazine	235–239	241–243	*244*, 350	134
Sulphamethazine	196–199	198–200	*203*, 275	
Sulphisomidine	243	243	*250*, 280	
Sulphamethoxy-pyridazine	180–183	181–183	*182*	275
Sulphathiazole	200–203	171–173	*172*, *208*	256
Succinyl sulphthiazole	188–195	196–199	130, *195*, 230, 275	303
Sulphisoxazole	192–195	194–197	*200*	220, 284, 310
Sulphacetamide sodium	252–256	255–258	145, *265*	340, 353
Sulphaguanidine	190–192	193	115, *195*	340
Sulphanilamide	164–166	160–164	*155*, 313	295
Sulphaphenazole	181–184	184–186	*185*	295
Phthalyl sulphthiazole	chars at 260	235	*235*, 284	314

gypsum; and visualizing agent: Ehrlich's reagent. For succinyl and phthalyl sulphathiazoles, the residue contained succinyl and phthalyl sulphanilamides. This is confirmed by hydrolyzing the residue with 0.1 *N* sodium hydroxide to remove the succinyl and phthalyl groups attached to N^4, so that the resulting sulphanilamide can react with Ehrlich's reagent.

Thermal analysis of sulphonamide mixtures

Figures 5 and 6 show collective DTA curves of binary mixtures (in the ratio 1 : 1) of sulphonamides. Figure 7 gives collective DTA and DTG curves of mixtures of three or four sulphonamides.

For binary mixtures, in some cases, both components are identified in their mixtures (Fig. 5, mixtures 1–6). In other mixtures (Figs 5–6, mixtures 7–22), only one component can be identified. Sulphanilamide is detected in mixtures 7–14, sulphacetamide sodium in mixtures 15–17, and sulphaguanidine in mixtures 18–22. Table 3 illustrates the endothermic and exothermic peaks used to detect the sulphonamides in the binary mixtures.

Mixtures of sulphonamides found in pharmaceutical preparations usually contain more than two components of sulphadiazine, sulphamerazine, sulphamethazine and sulphathiazole, the identification of which is not easy. Generally, the mixtures start to decompose at a lower temperature than do the individual compo-

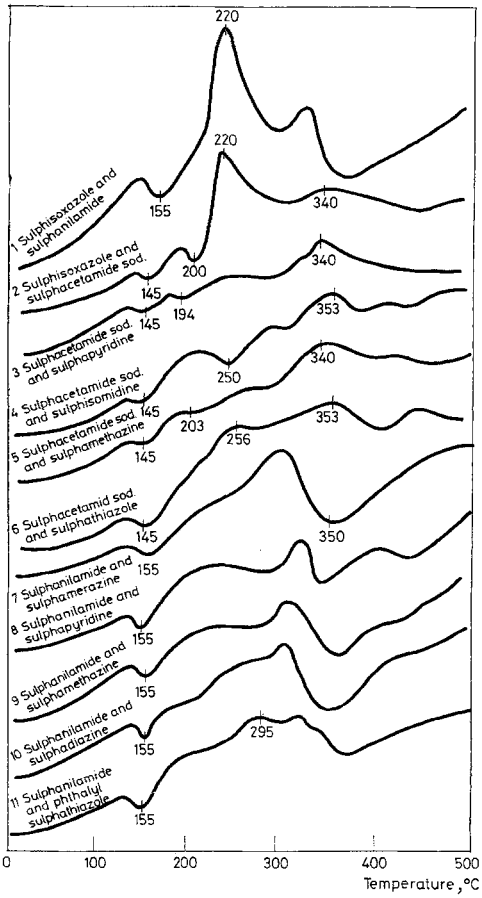

Fig. 5. DTA curves of binary mixtures of sulphonamides

Table 3

Endothermic and exothermic peaks used to detect the sulphonamides in their mixtures

Sulphonamides	Mixture no.	Characteristic peaks, °C	
		endothermic	exothermic
Sulphanilamide	1, 7–14	155, 313	295
Sulphacetamide sodium	2–6, 15–17	145, 265	340, 353
Sulphaguanidine	18–22	115, 195	340
Sulphisoxazole	1, 2	200	220
Sulphapyridine	3	194	
Sulphisomidine	4	250	
Sulphamethazine	5	203	
Sulphathiazole	6		256

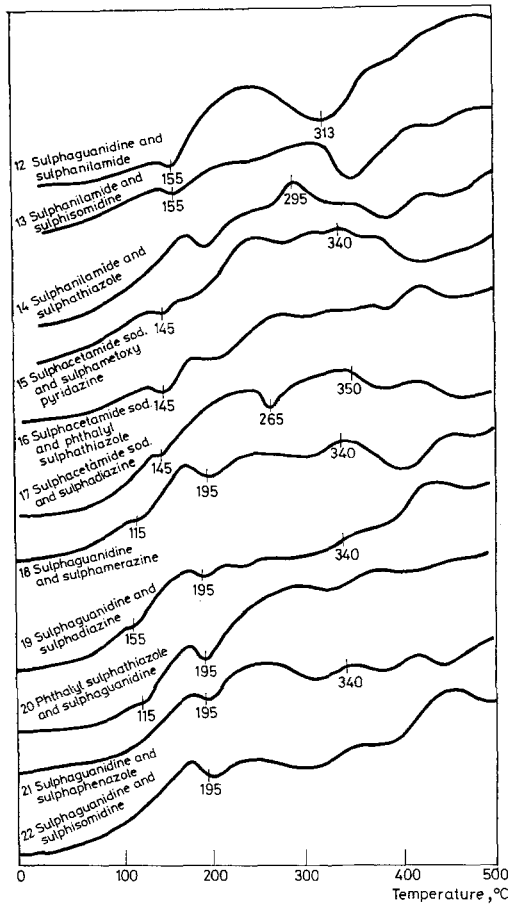

Fig. 6. DTA curves of binary mixtures of sulphonamides

nents (200–215°). The DTG curves of mixtures of three sulphonamides containing sulphadiazine show one main peak, followed by another small one as sulphadiazine yields two distinct DTG peaks (Fig. 7, mixtures 1, 2 and 4). The endothermic peak of sulphadiazine at 200° is also seen in some cases (Fig. 7, mixtures 1 and 2). Sulphamerazine is detected in its mixtures with two other components by its endothermic peak at 350° in the DTA curves (Fig. 7, mixtures 1, 2 and 3). A slight exothermic peak at 244° may also be seen (Fig. 7, mixtures 1 and 3) Sulphamethazine may be characterized in its mixtures by its endothermic peaks at 203 and 280° in the DTA curves (Fig. 7, mixtures 1 and 4). Sulphathiazole can be detected in its mixtures by either or both of its endothermic peaks at 172 and 208° (Fig. 7, mixtures 2, 3 and 4).

As these sulphonamides can not be accurately detected in the above mixtures, TLC analysis of mixtures of four sulphonamides is performed using different

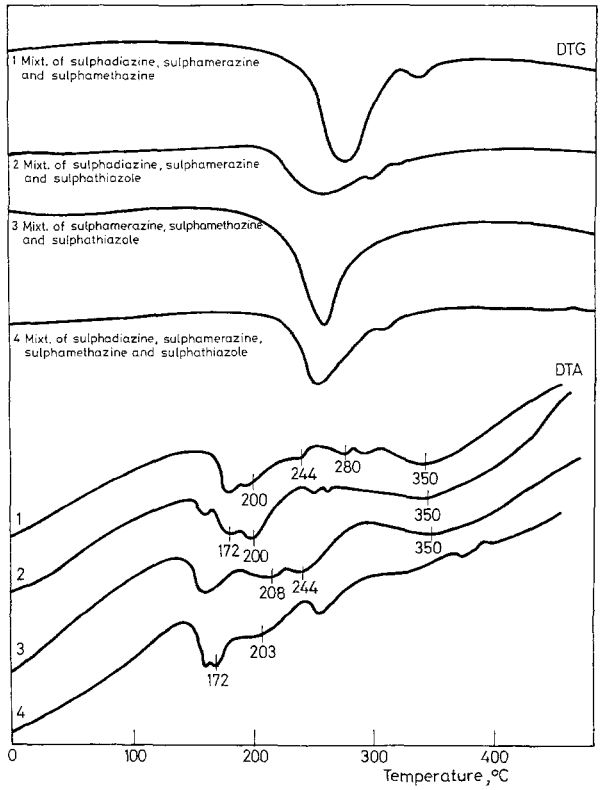

Fig. 7. DTG and DTA curves of mixtures of sulphonamides

systems. The best systems for separation of such mixtures are ethyl acetate : ether : chloroform in the ratios 70 : 20 : 10, 75 : 15 : 10 and 80 : 10 : 10, using plates coated with silica gel G and Ehrlich's reagent as visualizing agent. Ether also separates these mixtures, using either neutral plates of silica or alkaline plates (with 0.1 *N* sodium hydroxide to make the paste instead of distilled water in the ratio 1 : 2 (silica gel: 0.1 *N* sodium hydroxide)).

Conclusion

The characterization of sulphonamides could be achieved by thermal analysis, where the weight loss in each of the thermal reactions was quantitatively determined. It was found that, during heat treatment, the studied sulphonamides are first transformed to the parent compound, sulphanilamide. The melting points of sulphonamides, their water of crystallization contents and their thermal stabilities can be determined with the aid of their thermoanalytical curves. In the thermal analysis of sulphonamide mixtures, sulphanilamide, sulphacetamide sodium, sulphaguanidine and sulphisoxazole are easily detected in their mixtures.

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RÉSUMÉ — Quatorze sulfonamides ont été examinés par thermogravimétrie (TG), thermogravimétrie différentielle (TGD) et analyse thermique différentielle (ATD). Leurs réactions thermiques et leurs stabilités ont été étudées d'une manière approfondie. On a trouvé que les sulfonamides se transforment d'abord en sulfanilamides. Les points de fusion des sulfonamides ont été déterminés à partir de leurs courbes ATD et avec le microscope Kofler; les résultats ont concordé avec ceux de la littérature. La teneur en eau de cristallisation a été calculée à partir des courbes TG et TGD. L'analyse de deux, trois et quatre sulfonamides a été effectuée par analyse thermique et chromatographie en couches minces avec différents solvants.

ZUSAMMENFASSUNG — Vierzehn Sulfonamide wurden unter Anwendung der Thermogravimetrie (TG), der derivativen Thermogravimetrie (DTG) und der Differentialthermoanalyse (DTA) thermisch analysiert. Die thermischen Reaktionen und Stabilitäten wurden untersucht. Es zeigte sich, daß die Sulfonamide zuerst in Sulfanilamide umgewandelt werden. Die Schmelzpunkte der Sulfonamide wurden über ihre DTA-Kurven und mit dem Kofler-Mikroskop bestimmt, die Ergebnisse stimmten mit den in der Literatur angegebenen überein. Die Menge des Kristallwassers wurde aus den TG- und DTG-Kurven berechnet. Die Analyse von zwei, drei und vier Sulfonamiden wurde durch Thermische Analyse und Dünnschichtchromatographie unter Anwendung verschiedener Lösungsmittelsysteme durchgeführt.

Резюме — С помощью термогравиметрии (ТГ), термогравиметрии по производной (ДТГ) и дифференциального термического анализа (ДТА) исследованы четырнадцать сульфонамидов. Тщательно исследованы их устойчивость и термические реакции. Найдено, что первоначально сульфонамиды превращаются до сульфаниламида. Точки плавления сульфонамидов определены на основе их ДТА-кривых и с помощью микроскопа Кофлера. Полученные значения температур плавления согласуются с литературными. Исходя из ТГ- и ДТГ-кривых, вычислено количество кристаллизационной воды. Анализ двух, трех и четырех сульфонамидов проведен с помощью термического анализа и тонкослойной хроматографии, используя различные системы растворителей.