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THERMAL ANALYSIS METHODS IN THE STUDY OF SOME RETARD MACROMOLECULAR DRUGS

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ABSTRACT

A series of retard drugs have been synthetized by coupling on a polysaccharidic macromolecular support (xanthan), as well as on supports of the acrylic acid copolymer type. The active biological principle was represented by drugs such as acetazolamide, ampicilline, nitrofurane®, neomycine and streptomycine. The obtained drugs have been studied by thermal methods. Thus, information has been gathered upon the influence of the chemical nature of the support, and upon the type of the drug-support chemical bond on the thermal stability of the synthesized products. This investigation led to the settlement of a thermal method for dosing the coupled drug.

INTRODUCTION

Drug retardation on natural /1-2/ and synthetic /3-4/ macromolecular supports has been largely developed lately, as a consequence of the multiple advantages evidenced by this method, especially in chemotherapy. The process is performed by drug coupling on macromolecular supports, accompanied by the formation of labile - covalent or ionic - bonds. The most widely used supports are polysaccharides and their derivatives (xanthan, carboxymethylcellulose, starch, dextrane /5-7/) as well as syn-

thetic polymers - copolymers of the acrylic acid, hydroxyethyl methacrylate, etc /8-9/, their choice selection being determined - mainly - by their biocompatibility.

The present paper describes the thermal behaviour of some drugs (acetazolamide, ampicilline, nitrofurane^{R}, neomycine, streptomycine), in free form as well as retarded on xanthan, poly(styrene-co-acrylic acid) and poly(vinylic alcohol-co-acrylic acid).

EXPERIMENTAL

The thermal curves were recorded on a Paulik - Paulik - Erdey (MOM Budapest) apparatus. The runs were made with samples of 45 - 50 mg, heated in air at a rate of 10°C/min, within the temperature range 20 - 500°C. The activation energies and the reaction orders for the destruction processes were calculated by the Coats - Redfern method /10/ with a Felix CE - 32 computer.

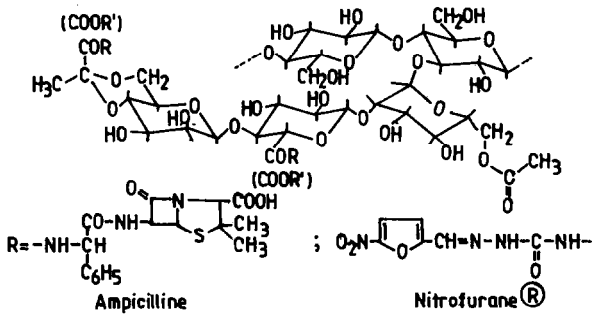
The thermal behaviour was characterized by taking into account the degradation temperature (Td), referred to as the temperature where weight loss begins, the temperature ranges of the destruction stages as well as the weight loss percentage for every stage.

RESULTS AND DISCUSSION

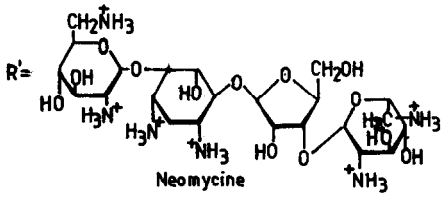
The chemical structures of the drug supports and the nature of the drug - support bond determine their thermal behaviour.

The support analyzed in this study was xanthan, taken in its natural form (as a salt of Na, K, Ca) and also decationized, as well as two synthetic copolymers: poly(styrene-co-acrylic acid) and poly(vinylic alcohol-co-acrylic acid), on which there have been coupled - through covalent bonds - ampicilline and

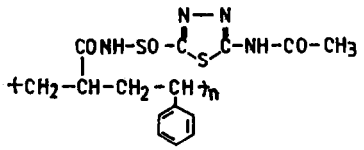
nitrofurane® (on xanthan), acetazolamide (on the poly(styrene--co-acrylic acid) copolymer) and - through ionic bonds - neomycine (on xanthan) and streptomycine on the poly(vinylic alcohol -co-acrylic acid) copolymer.



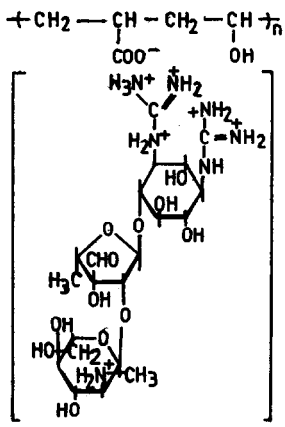
Ampicilline ; Nitrofurane®



Neomycine



Acetazolamide retard



Streptomycine retard

In the case of ampicilline (Fig. 1, curve 2) the thermogramme is being characterized by a weakly endothermal stage within the temperature range of 140 - 220°C, and a weight loss of 22 % (stage II) (Table 1). As in the 155 - 220°C temperature range xanthane is stable (the weight loss being about 2 - 2.5%), stage II on the derivatogramme of xanthan - retarded ampicilline (weight losses of 9 %) (Fig. 1, curve 3) has thus to be correlated with stage II from the ampicilline derivatogramme - this idea being also supported by the weakly endothermal aspect of the DTA curve, in both cases. Through calculations, one may obtain a percentage of about 30 % ampicilline grafted on the support, which is in agreement with the value found through the chemical method /11/.

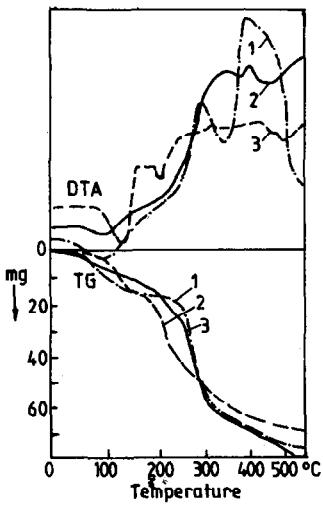


Fig. 1. DTA and TG of xanthan (1), ampicilline (2) and ampicilline retarded on xanthan (3).

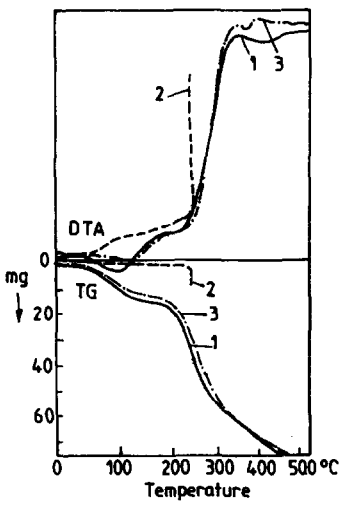


Fig. 2. DTA and TG of decationized xanthan (1), nitrofurane® (2) and nitrofurane® retarded on decationized xanthan.

Thermogravimetric analysis of nitrofurane® (Fig. 2, curve 2) shows an explosive decomposition at 230°C. Thermogrammes obtained for the support (decationized xanthan - Fig. 2, curve 1) and for

TABLE 1

Thermal properties of supports, drugs and retarded drugs

Starting component	Thermogravimetric data					
	Td (°C)	Degradation steps	Temperature range (°C)	Weight losses (%)	Activation energy (Kcal/mol)	Reaction order
1	2	3	4	5	6	7
Xanthan	50	I	50 - 185	15.5	12.9	1.5
		II	210 - 315	42.5	31.4	0.0
		III	315 - 475	15.5	-	-
Ampicilline	55	I	55 - 140	14.0	9.9	0.0
		II	140 - 220	22.0	20.1	0.0
		III	220 - >500	-	-	-
Ampicilline retarded on xanthan	55	I	55 - 155	9.0	13.6	2.1
		II	155 - 220	9.0	40.1	2.5
		III	225 - 340	42.0	29.3	1.0
		IV	340 - >500	-	-	-
Xanthan decationized	45	I	45 - 160	13.5	13.1	1.8
		II	160 - 345	47.0	20.9	0.0
		III	345 - >500	-	-	-
Nitrofuran®	230	I	230 -	-	-	-
Nitrofuran® retarded on xanthan	50	I	50 - 140	10.5	12.0	1.6
		II	155 - 375	53.5	19.2	2.5
		III	375 - >500	-	-	-
Acetazolamide	235	I	235 - 280	37.0	-	-
		II	280 - 330	22.0	-	-
		III	330 - 440	16.0	-	-
Poly(styrene -co-acrylic acid)	290	I	290 - 425	90.0	-	-
		II	455 - 550	10.0	-	-
Acetazolamide retarded on poly(styrene-co-acrylic acid)	125	I	125 - 220	9.0	-	-
		II	220 - 260	2.0	-	-
		III	260 - 435	79.0	-	-
		IV	465 - 570	10.0	-	-
Neomycine sulphate	65	I	65 - 190	17.5	11.5	2.2
		II	190 - 240	13.0	88.2	1.7
		III	240 - 355	36.0	55.3	2.5
		IV	355 - >500	-	-	-
Neomycine retarded on xanthan	45	I	45 - 150	14.0	11.6	1.8
		II	180 - 240	14.0	28.9	0.3
		III	240 - 330	36.0	72.4	2.5
		IV	330 - >500	-	-	-
Poly(vinylic alcohol-co-acrylic acid)	45	I	45 - 155	8.0	13.0	2.5
		II	155 - 460	60.0	14.8	2.5
		III	460 - >500	-	-	-
Streptomycine sulphate	50	I	50 - 190	11.5	13.0	2.1
		II	190 - 230	10.0	53.5	1.1
		III	230 - 390	36.5	9.2	0.0
		IV	390 - >500	-	-	-
Streptomycine retarded on poly(vinylic alcohol-co-acrylic acid)	40	I	40 - 135	15.0	13.2	2.5
		II	135 - 205	10.0	49.2	2.5
		III	205 - 285	15.0	-	-
		IV	285 - >500	-	-	-

nitrofurane® retarded on xanthan are not different with regard to the scope of the TG and DTA curves; it is only the second stage of the thermal decomposition that evidences a weight loss higher than 6.5 % - in the case of the retarded drug.

The thermogravimetric curve of neomycine sulphate (Fig. 3, curve 2) shows a weight loss stage (the second) between 190 and 240°C, which is characterized by a higher reaction rate and a weight loss of 13 %. The support (xanthan) does not loose

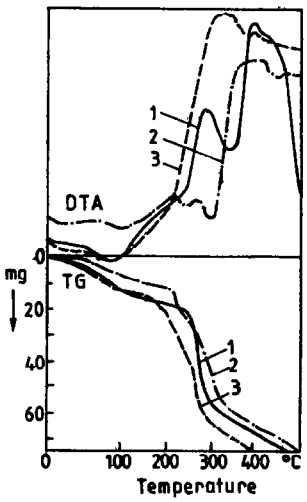


Fig. 3. DTA and TG of xanthan (1), neomycine sulphate (2) and neomycine retarded on xanthan (3).

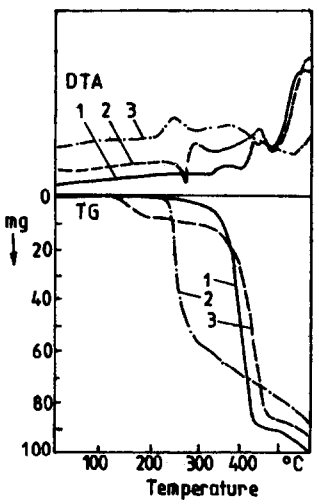


Fig. 4. DTA and TG of poly (styrene-co-acrylic acid) (1), acetazolamide (2) and acetazolamide retarded on poly (styrene-co-acrylic acid) (3)

its weight within 190 - 215°C, yet, from 215°C on, a significant process of decomposition occurs, going on up to 315°C (Fig. 3, curve 2). Due to the superposition of the two processes, of decomposition - of the support and of neomycine sulphate - the exact establishment of the drug's part in the global weight loss within this temperature range is not possible. Nevertheless, it is obvi-

ous that neomycine sulphate is present in this structure, the loss weight being much stronger than that characterizing the support.

Thermogravimetric and thermodifferential analysis was performed on a coupling product having an acetazolamide content of 11.5%; at the same time, the free drug and the support polymer have been analysed. The acetazolamide thermogramme evidences the fact that weight losses are manifested beginning at a temperature of 235°C, being spaced out in four steps (Fig. 4, curve 2). The support copolymer is being decomposed starting from 290°C in two steps (Fig. 4, curve 1). The coupling product begins to losse weight starting from 125°C. In the first stage, weight losses up to 9% occur in the temperature range of 125 to 200°C, being accompanied by a slight endothermal effect. In the second stage (220 - 260°C), losses - of about 2 % - are accompanied by a considerable exothermal effect. These two stages may be attributed to drug detachment off the support and its decomposition. Thus, the drug ratio in the coupling product is about 11 %. The following two decomposition stages correspond to the support degradation. The coupling product, having a maximum drug content, has been tested in vivo, showing retard diuretic activity /11/.

The poly(vinylic alcohol-co-acrylic acid) copolymer is being used as support in the retardation of streptomycine. Its thermogramme (Fig. 5, curve 1) evidences that, up 155°C, it is relatively stable, the weight less being only 8 % (stage I, temperature range 45 - 155°C) On the whole, the copolymer has three decomposition stages. In stage II, up to a temperature of 460°C, losses are significant up to 60 %.

Streptomycine sulphate has four stages of thermal decomposition (Fig. 5, curve 2). which are to be found, too, on the derivatogramme of retarded streptomycine (Fig. 5, curve 3). Although the

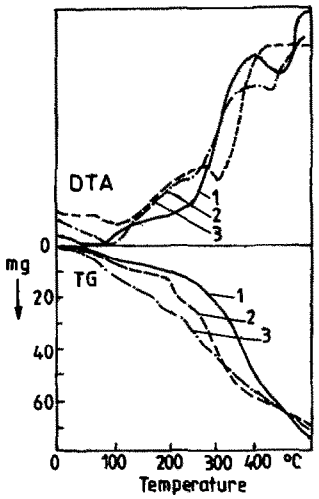


Fig. 5. DTA and TG of poly(vinylic alcohol-co-acrylic acid) (1), streptomycine sulphate (2) and streptomycine retarded on poly(vinylic alcohol-co-acrylic acid) (3)

slope of the TG curve is similar for streptomycine and for its retarded form, the DTA curve of retarded streptomycine is much similar in its aspect to that of the copolymer used as support (Fig. 5.

One may thus conclude that, in all examined cases, the methods of thermal analysis demonstrate the advantages of drug coupled on supports. The thermal stability of retarded drugs is given by the thermal stability of the supports and not by that of the starting drugs.

CONCLUSIONS

Thermodifferential analysis of retarded drugs led to the conclusion that the slope of DTA and DTG curves depends upon the structure of the support and of the drug. In certain situations, where the superposition of the decomposition stages does not occur, as it is the case of neomycine retarded on xanthan and that of acetazolamide on the poly(styrene-co-acrylic acid) copolymer, the method of thermodifferential analysis may be applied in establishing the amount of drug bound on the support.

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