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Polymeric drugs carriers of methacrylic and acrylic derivatives

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Summary

2-Amino-thiazole reacts with methacryloyl or acryloyl chloride to give amides which are polymerized. Hydrolyses of polymers have been studied with and without enzymatic catalysis in a synthetic gastric liquid.

Introduction

Galenic forms, able to control the drug release in stomach, can be prepared by dispersing the drug in a biocompatible polymer[1] or by attachement to a polymeric matrix as well as by syntheses of branched monomer with the drug followed by a polymerization or copolymerization. Various drugs have been attached to polymeric matrices such as procaïne[2], atropine[3], aspirin[4] and quinidine[5], and the main used polymers were polyethylene glycol, polyvinylchloroformiate or polyvinylalcohol. The synthesis of a monomer with a pendant drug is more scarcely described : chloramphenicol has been attached through an acetal function to a methacrylic derivative and then copolymerized with 2-hydroxyethyl methacrylate[6]. Methacrylic derivatives have also been proposed as drug carrying monomers[7]. For this study we have chosen to prepare an amide function synthesized by reaction of methacryloyl or acryloyl chloride with the 2-amino-thiazole which was formely used as a antithyroïd agent[8]. Preparations of monomers and polymers are described. The drug release in synthetic gastric liquid (pH = 1,2) with or without a enzymatic catalysis has also been studied.

Experimental

The glass transition of polymers were measured with a D.S.C. 101 Setaram : Mass sample 10-15 mg, heating rate 10°C/min. IR Spectra of monomers and polymers were measured with a Beckmann Acculab Spectrometer.

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^{1}H NMR and ^{13}C NMR spectra were recorded using respectively a Perkin-Elmer Hitachi R. 24 (60 MHz) and a Brucker (75 MHz) apparatus. Samples of monomers were dissolved in $CDCl_3$ (5 % and 15 % weight/volume for ^{1}H and ^{13}C). The drug release from polymers has been carried out by soaking samples of product (50 mg) in synthetic gastric liquid (100 ml) with pH = 1,2 at 37°C (1000 ml of aqueous solution ; 80 ml HCl 1N ; 2 g NaCl). Enzymatic catalysts are 1) Albumin 2 g/liter 2) Albumin 2 g/liter and Pepsin (580 units/mg solid), 2 g/liter 3) Pepsin (580 units/mg solid), 2 g/liter.
The rate of the drug released from the polymer has been measured by using a UV Spectrometer Hitachi U. 1100.

Preparation of monomers 2 a and 2 b

Methacryloyl chloride 1 a (0,04M - 4,2 g) in 20 ml of tetrahydrofuran (THF) is slowly added in a stirred solution of 2-amino-thiazole (0,04M - 4 g) and triethylamine (0,04M - 4,04 g) in 120 ml of THF. The mixture is stirred during 20 hours at 0°C then filtered and evaporated with a rotavapor. A yellow product is obtained after precipitation with hexane (yield 52 %). The procedure is similar for the preparation of N-acryloyl-2-amino-thiazole (2 b) (yield 85 %).

Preparation of polymers 3 a,b

The syntheses of polymers were performed in a sealed tube : the monomers (2g) are dissolved in 2 ml of THF and heated with 2 % in weight of Azobisisobutyronitrile at 70°C during 20 hours. The polymers are filtered then washed with methanol and dried. The yields are close to 75 % and 90 % for 3 a and 3 b. Products are insoluble in all organic solvents.

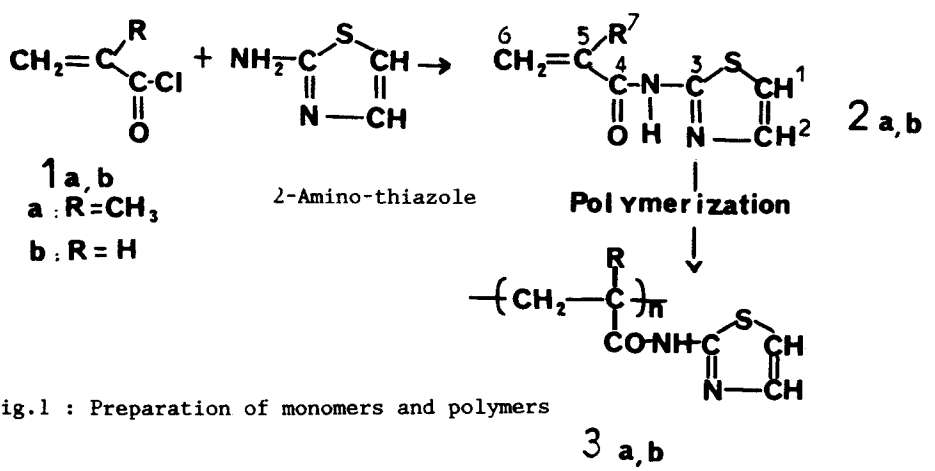

Fig.1 : Preparation of monomers and polymers

Characterization of monomers 2 a,b and polymers 3 a,b

Microanalyses of monomers 2 a,b and polymers 3 a,b are in agreement with the attempted structures. The melting points of 2 a and 2 b are respectively at 101°C and 129°C.

IR spectra show absorptions at 1670 cm^{-1} (C=O), 1630 cm^{-1} (C=C) for 2 a and 2 b, and 1680 cm^{-1} (C=O) for polymers 3 a and 3 b. The glass transition temperature are 98°C (3 a) and 124°C (3 b).

NMR spectra (^1H) of monomers 2 a,b are given in table 1.

Table 1 : Chemical shifts in the ^1H NMR of 2 a,b*.

	2 a	2 b
$\underline{CH_3}-\overset{|}{C}=$	2,12 (s)	-
$\underline{CH_2}=\overset{|}{C}-$	5,66 (d) 5,93 (d)	5,66 (2d)
$CH_2=\underline{CH}-$		6,43 (2d)
-CH=CH- (Thiazole nucleus)	7,02 (d) 7,45 (d)	7(d) 7,06 (d)
$-\overset{|}{N}H$	7,08 (s)	7,62 (s)

* s = singulet 2 d = pair of doublets.

NMR spectra of 2 a,b are given in table 2

Table 2 : Chemical shifts in the ^{13}C NMR of 2 a,b.

	2 a	2 b
C_1	113,35	114,05
C_2	137,08	136,32
C_3	160,14	160,30
C_4	166,97	163,32
C_5	121,93	128,94
C_6	139,25	130,106
C_7 (R=CH_3)	18,60	—

The measurements of molecular masses and the recording of NMR spectra were not possible because of the insolubilities of polymers 3 a,b in all organic solvents.

Results and discussion

2-Amino-thiazole has been chosen as a model drug because the UV absorption (256 nm), in a synthetic gastric liquid, is quite different from those of albumin (204 nm) and pepsin (205 nm). The results of drug release at pH 1,2, without enzymatic catalysis are given in table 3 for monomer 2 a and polymer 3 a and 3 b.

Table 3 : % of released drug in monomer 2 a and in polymers 3a,b.

	time (mn)					
	5	10	30	60	120	240
2 a	9,30	10,68	13,75	16,75	19,50	22,50
3 a	0,88	1,1	1,5	1,9	2,6	3,6
3 b	0,6	0,9	1,9	2,9	4,27	5,35

These results describe a very slow hydrolysis of amide function in synthetic gastric liquid without enzymatic catalysis. In fact, it seems probable that enzymes such as albumin and pepsin are present in the gastric liquid during the ingestion of food[9].

Consequently, we have prepared a gastric liquid with albumin and pepsin to study the rate variation of hydrolysis. These results are given in table 4 and fig 2.

Table 4 : Percentage of released drug in polymer 3 b with enzymatic catalysis.

	time							
Catalysis	5mn	10mn	30mn	60mn	120mn	140mn	24h	72h
Albumin 2g/l	2,1	2,5	3,42	4,30	5,25	6,1	10,6	13,4
Pepsin 2g/l	3,11	4	5,2	6,1	7,2	8,1	13	15,25
Pepsin 2g/l and Albumin 2g/l	7,0	7,7	9,0	9,80	10,15	10,7	13,50	15,25

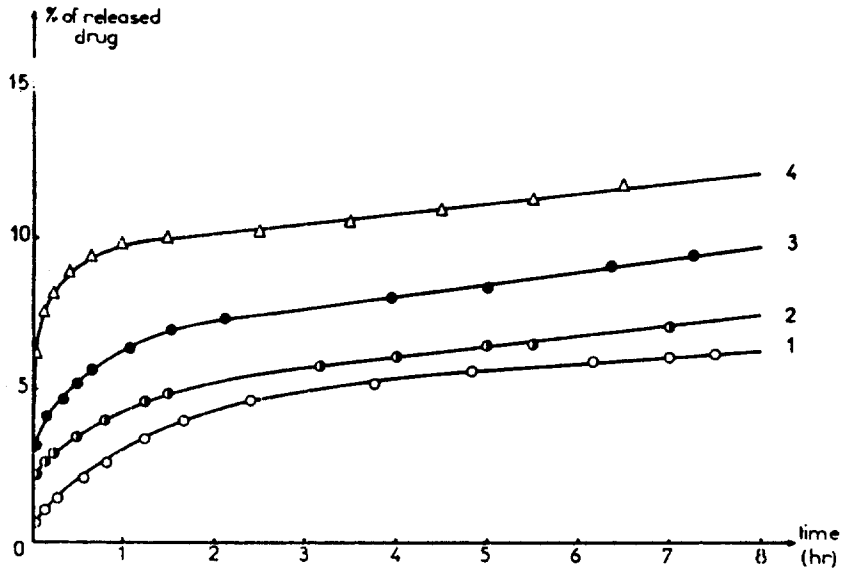

Fig.2 : Kinetic of released drug from polymer 3 b :
1) Without catalysis 2) with albumin 3) with pepsin
4) with pepsin and albumin

From these experimental results, some conclusions are worth pointing out :
1) The percentage of released drug is relatively high with the monomer and very low with the polymers 3 a,b without catalysis ; it is well known that chemical reactions with polymers are more difficult and longer than with monomers or oligomers.
2) Without catalysis, the rates of hydrolysis are small and less than 10 % of drug were characterized.
3) Enzymatic catalysis with pepsin and albumin, give an increased percentage of released drug at the beginning of the study, (up to 240 minutes) but subsides after some hours.
4) No chemical kinetic equations can describe the drug release from the polymers, in powder and insoluble form, the liquid enters the polymers and a gel is formed. The kinetics are probably partially controlled by diffusion as shown by the square root of time dependance of the amount of drug released[10]. The process could be described as follows : the liquid enters the polymers (formation of a gel), reacts with part of polymers and then enables the drug to diffuse out of the polymer. Of course the above-

described enzymes also diffuse through the polymer, and play their role as a catalyst.

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