Polymer Bulletin 23, 331–334 (1990)

Polymer Bulletin

Hydrolyses of polymeric Schiff bases in acidic medium

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Summary

Three polymeric Schiff bases have been synthesized from corresponding monomers and prepared by means of a radical polymerization. These polymers have relatively low molecular masses and their hydrolyses, with release of amines, have been studied in a synthetic gastric liquid of pH = 1,2.

Introduction

Drug delivery systems with macromolecules as carriers have been object of much attention for the last few years$^{1)}$ and several kinds of polymers, for buccal absorption, can be used : a) The drug is dispersed in a biocompatible polymer and the drug release occurs by diffusion$^{2)}$ or osmosis$^{3)}$, b) The drug is attached to a polymeric matrix or to a monomer then polymerized or copolymerized$^{4)}$. The attachment of drug to a polymerizable monomer can be carried out directly or by means of spacer groups to favour the hydrolytic release of the drug moiety$^{5)}$. Vinylbenzaldehyde 2 seems to be a valuable monomer because constitued by an ethylenic chain, substituted by a phenyl group as a spacer and with an aldehyde function to attach an amine function. This aldehyde is prepared in one step from vinylbenzylchloride 1 (mixture meta/para, 3/2) commercially available. Only some works have been devoted to the polymeric Schiff bases or imines : anionic polymerization has been carried out by A.Hirao et al for the imine of vinylbenzaldehyde with cyclohexylamine$^{6)}$, H.Kamogawa et al have described some polymeric imines derivated from vinylbenzaldehyde with heavy amines$^{7)}$.
The syntheses of three polymeric Schiff bases in which the amine groups are respectively, aniline, benzylamine and phenylethylamine and their hydrolyses in acidic medium, are now given.

Experimental

Molecular masses of polymers have been measured with a Knauer apparatus and Ultra Styragel columns 10^4 Waters (0,7 ml/min). Polystyrene standards have been used for the calibration. ^{1}H NMR spectra of monomers were recorded by using a Perkin-Elmer Hitachi R 24 A. Samples of monomers have been dissolved in $CDCl_3$ (5 % weight/volume). The amine release study has been carried out by soaking samples of product (50 mg) in synthetic gastric liquid (100 ml) with pH = 1,2 at 37°C. The synthetic gastric liquid is prepared by dissolving 80 ml HCl 1N, 2 g NaCl in 1000 ml of distillated water. The rate of drug release from the polymer has been measured by using a U.V. Spectrometer Hitachi U 1100. Vinylbenzaldehyde 2 has been prepared according to a known procedure$^{8)}$ by using Sommelet reaction, with hexamethylene tetramine and vinylbenzylchloride. Schiff bases have been prepared by

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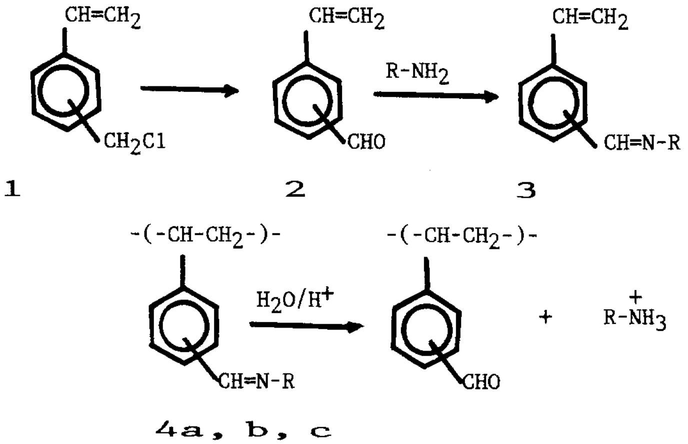
*To whom offprint requests should be sent heating a mixture of aldehyde 2 (70 mmol), amine(aniline, benzylamine or phenylethylamine : 77 mmol), 2,6-Di t-butylcatechol (2 mg) and 50 mg of p. toluenesulfonic acid (50 mg) as a catalyst in benzene (100 ml). After azeotropic removal of water (3 hours), the solution has been cooled, carefully neutralized with an aqueous sodium hydroxyde solution (1N), dried and the solvent has been evaporated. The imine 3a ($R=C_6H_5$) can be distillated under vacuum but distillation with $R=C_6H_5CH_2$ or $C_6H_5CH_2CH_2$ produces polymers. Monomers 3a, b, c have been characterized by their ^1H NMR spectra (peaks at 8 ; 7,85 and 7,6 for the -CH=N- bonds of 3a, b, c).



a) $R=C_6H_5-$; b) $R=C_6H_5-CH_2-$; c) $R=C_6H_5-CH_2CH_2-$

Fig. 1 : Préparation of monomers and polymers.

The syntheses of polymers 4a, b have been performed in a sealed tube in bulk by using azobisisobutyronitrile (AIBN) as an initiator (2 % in weight). After 20 hours at 70°C the raw polymer is solubilized in chloroform, precipitated by hexane, then dried . Preparation of 4c needs a transfer agent and benzene as a solvent : two gramms of monomer 3c are heated during 30 minutes with 1 ml of benzene, 1 mg of n-butylthiol as a transfer agent, and 100 mg of A.I.B.N. The yields of polymers 4a, b, c are close to 50 %. Microanalyses of polymers 4a, b, c are in good agreement with the attempted structures. The polymers 4a, b, c, in powder form, are insoluble in water. The molecular masses are given in tab. 1.

Tab. 1. Molecular masses of polymers 4a, b, c.

Polymers	Mn	Mw	Mw/Mn
4a	26 000	105 000	4,04
4b	11 000	36 000	3,27
4c	7 500	14 000	1,86

Results and discussion

Imines or Schiff bases are well-known for their easily hydrolysable properties under acidic conditions. These outstanding characteristics can be utilized for the syntheses of the readily hydrolyzable polymers which might find their use in liberating their functional groups gradually. The main results of hydrolyses studies are given in tab. 2.

Tab. 2 : Percentage of released amine by hydrolysis of polymers 4a, b, c in acidic medium of pH = 1,2.

Times (hours)	0,5	1	2	3	4	5	6	8
4a	26	31	37	40	42	43	44	45
4b	19	29	46	57	66	73	79	88
4c	15	18	26	37	52	66	77	88

The kinetics of released amines from polymer 4a, b, c are given en Fig 2 :

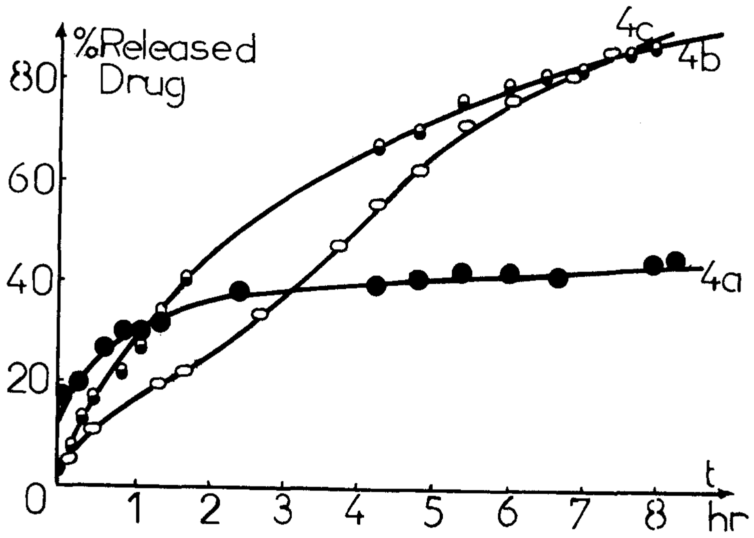


Fig.2 : Kinetic of released drug from polymers 4a, b, c in acidic medium (pH = 1,2).

From these experimental results, some conclusions are worth pointing out : 1) The percentage of released amine is high with the polymer 4b and 4c and lower with 4a. 2) The hydrolysis reaction is a chemical modification of a polymer, the rate depends on the molecular masses of the macromolecule, the reaction is fast when the molecular weight is low (polymer 4b and 4c) and lower when the masses are high (polymer 4a), 3) The hydrolysis rate also depends on the nature of the ammonium ion : the mechanism of hydrolysis of a Schiff base can be summarized as follows :

$R\text{-}CH{=}N\text{-}R' + H_2O \xrightleftharpoons{H^+} R\text{-}CHO + R'\text{-}NH_3$. The anilinium cation

$C_6H_5\overset{+}{N}H_3$ is probably the most stable comparatively to the cation $C_6H_5CH_2CH_2\overset{+}{N}H_3$ and $C_6H_5CH_2\overset{+}{N}H_3$, but it is the most difficult to form, 4) Lastly, no chemical kinetic equation can describe the drug release from the polymer, the process being controlled largely by transient diffusion and can be described as follows : the liquid enters the grains of the insoluble polymer, provoking a swelling of the polymer. Then the liquid located inside the grains reacts with the Schiff bases, and then the product of reaction diffuses out of the grain. The main proof shown for this diffusional process is the square-root time dependance of the amount of released drug$^{9)}$.

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Accepted January 12, 1990 C