

Second Step Modification of Epoxidised Polymers#.

5. Systems Allowing Release of Naphthylacetic Acid from Epoxidised Polyisoprene and Liquid Natural Rubber

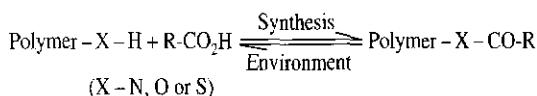
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A polymeric support containing free or linked naphthylacetic acid (NAA), a stimulator for the production of latex by Hevea can be obtained from epoxidised synthetic 1,4-polyisoprene or liquid natural rubber (LNR). Crosslinking of emulsified epoxidised polymers containing free or bound NAA by diacids or anhydrides catalysed by the tetrabutylammonium salt of the corresponding diacids leads to polymeric particles containing free NAA. Hydrolysis of NAA derivatives of epoxidised 1,4-polyisoprene and epoxidised LNR has been performed in basic media. This particular formulation leads to a high initial rate of liberation.

In the agricultural domain, half of the fertilisers introduced for plants is lost, destroyed by micro-organisms or ambient factors^{1, 2}. This explains the increasing amount of research dealing with sustained release of such products. Among the proposed solutions, polymeric supports and micro-encapsulation are the methods chosen in this study. Drugs, plant growth stimulators, insecticides, herbicides, and pesticides can be employed³ with this technology.

Polymers with bioactive molecules linked by covalent bonds can be used as dosage forms allowing a controlled release through hydrolysis in the same way as for polymeric drug carriers.

In the case of molecules with a carboxylic functional group, the linkage to the polymer can be obtained according to the following scheme^{1, 3}:



Many polymers have been used, for example polysaccharide (chitin, cellulose, dextran) bearing herbicides whose hydrolysis has been studied^{4, 5}.

In the case of polyvinyl alcohol acetylated by 2,6-dichlorobenzaldehyde (a strong herbicide), the initial hydrolysis rate is inversely proportional to the extent of acetylation⁶.

For plant growth stimulators^{7–10}, hydrolysis of nicotinoyl ester from amylose modified by nicotinoyl chloride is improved by the hydrophilic character of the modified polymer, temperature and pH⁸.

Hydrolysis of copolymer (acrylamides, acrylates) bearing plant growth stimulators, naphthylacetic and indole acetic acid, has been followed by liquid chromatography and UV detection⁹. The hydrolysis depends on the nature of the stimulator, composition of the copolymer, molecular weight and micro-structure. Moreover, increase of the hydrophilic sequence length in copolymers increases the rate of release of these molecules^{9, 10}.

Part 3: cf. ¹⁸

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On the other hand, release of a fertiliser encapsulated by natural rubber is another interesting technique¹¹. The results obtained show that the rate of release depends on the thickness of the rubber film and nature of the rubber. On maize and *Hevea*, improved results were obtained compared to the traditional method.

In the case of urea in a natural rubber matrix², solubility of the fertiliser in water is proportional to the concentration of urea in the matrix and it increases with temperature. However, there is no difference when natural rubber is vulcanised at 60% or 90% of the theoretical maximum.

By the encapsulation process, urea particles have been enclosed in a sulphur matrix or within a membrane allowing its controlled release¹². Polymers have also been used¹³.

When the active species is dispersed in a polymer, a monolithic system is formed¹⁴. Its release is controlled either by diffusion through the support or by dissolution or degradation (e.g. hydrolysis) of the support. If the active species is linked to the matrix by a hydrolysable chemical bond, hydrolysis must also be considered.

Some products have been commercialised as shown in (Table 1). *Hevea* latex has allowed the encapsulation of a water-soluble fertiliser,

such as urea, and the matrix works as a dosage form. In this case, rubber technology has been applied².

Epoxidation of polyisoprene provides a means to reinforce the strength of particles through crosslinking of the polymer under mild conditions. Crosslinking of epoxidised polyisoprene can be obtained by the action of bifunctional reagents^{15, 16}, such as carboxylic anhydrides catalysed by tertiary amines¹⁷.

This reaction is applied to epoxidised polyisoprenes containing naphthylacetic acid (NAA) dispersed in or linked to the polymer¹⁸ in emulsion to obtain particles whose size is controlled by the emulsion parameters. The general scheme (*Scheme 1*) is given below in the case of epoxidised liquid natural rubber (ELNR).

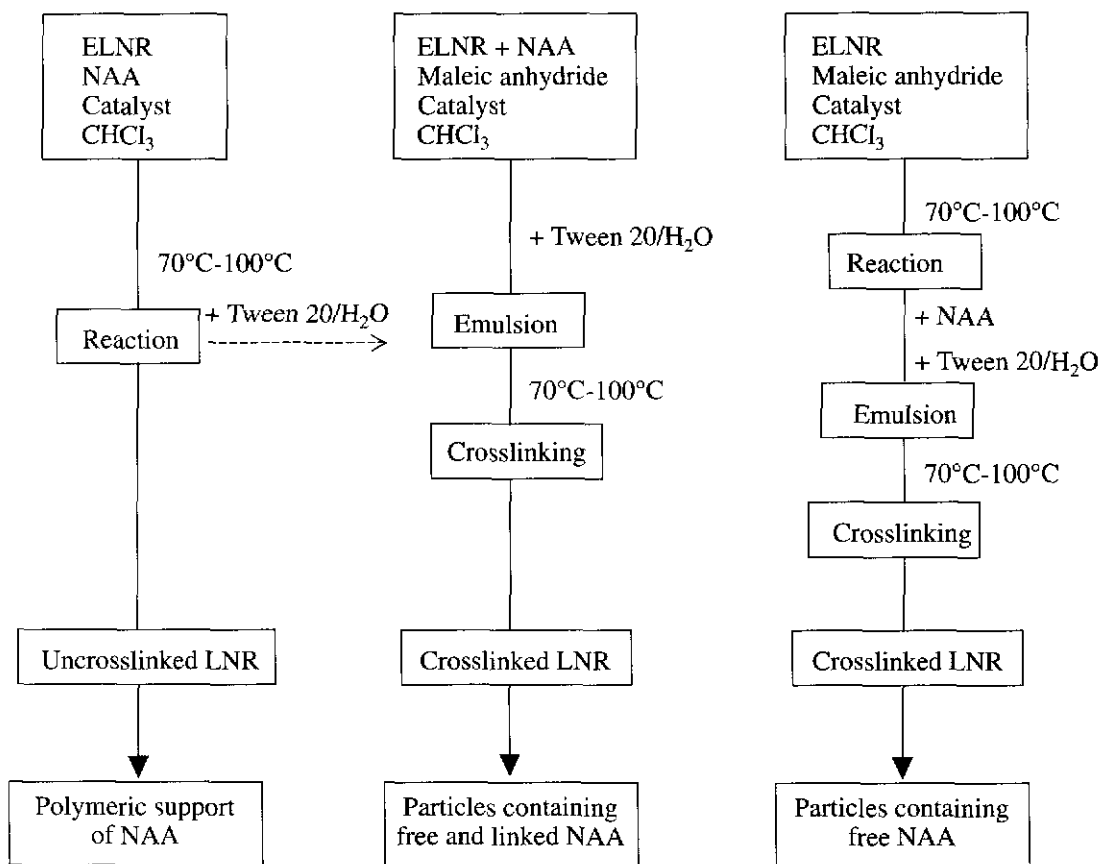
EXPERIMENTAL

The solvent (CHCl_3) was distilled before use. NAA was recrystallised twice from water.

Tetrabutylammonium salts used as catalysts were prepared by neutralising the corresponding acids by tetrabutylammonium hydroxide in methanol solution (Aldrich), followed by evaporation of the solvent and drying under vacuum at 60°C. Polymers were prepared as described by Soutif *et al.*¹⁸

TABLE 1. SOME COMMERCIAL PRODUCTS ALLOWING CONTROLLED RELEASE¹³

Trade name	Company	Property
NOFOUL	B.F. Goodrich	'Antifouling'/rubber matrix or membrane
NO-PEST STRIP	Shell	Insecticide/matrix
HERCON DISPENSER	Health-Chem	Pesticide/laminated system
PRECISE	3M	Micro-encapsulated fertiliser
OSMOCOAT	Sierra	Micro-encapsulated fertiliser
PENNCAP-M	Pennwalt	Micro-encapsulated insecticide (methyl parathion)
OCCUSERT	Alza	Pilocarpine/laminated system
PROGESTASERT	Alza	Progesterone/reservoir system
BioMET SRM	M & T	Molluscicide/matrix
INCRACIDE E-51	International Copper Research Association	Molluscicide/matrix



Scheme 1

Reaction of Acids and Anhydrides with Epoxidised Polyisoprene

Reactions were carried out in glass screw tubes (total volume 15 ml) with magnetic stirring. The tubes containing the reagent, the catalyst, the polymer and the solvent (CHCl_3) were held by a rotating support in an oil bath at the desired temperature. At the chosen reaction time, the content of the tube was diluted with methanol before titration of unreacted acid by 0.5 M tetramethylammonium hydroxide in methanol, monitored with a Metrohm potentiometer (Impulsomat 614, Dosigraph 625, pH-Meter 632 and Dosimat 655). The reaction yield ($X\%$ in Table 2) is the equivalent of diacid or dianhydride reacted at time t .

NAA-EPIP and NAA-ELNR used further correspond to a NAA content in the polymers of:

- 92 mg/g of product (NAA-EPIP, prepared from epoxidised and modified 1,4-polyisoprene),
- 126 mg/g of product (NAA-ELNR, prepared from epoxidised and modified LNR).

Preparation of Crosslinked Particles from Epoxidised Polyisoprene

The polymer and maleic anhydride solution in chloroform was stirred at 70°C for 1 h in the presence of tetrabutylammonium salt. Emulsion was then carried out by dropping

(for 10-20 min) the solution in the aqueous phase containing a non ionic emulsifier (Tween 20) with stirring. The reaction was maintained at 70°C for 23 h before isolating the particles, by filtration and washing with water.

Crosslinking of Epoxidised 1,4-polyisoprene

A preliminary study of the reaction between diacids or anhydrides with ELNR has been conducted in chloroform solution at 70°C, catalysed by the tetrabutylammonium salt of diacids (Table 2). Diacids and anhydrides are sometimes sparingly soluble in chloroform, which explains the poor results observed in some cases.

The best results have been obtained with maleic anhydride and malonic acid, with 23% yield after 72 h of reaction. Gelation, leading to insolubilisation of the polymer, occurs when yields are above 15% in the case of anhydrides. However, results show a marked slow down of the reaction rate with time: the amount of reacted acid or anhydride seems to be close to a maximum after 72 h of reaction. This can be explained by secondary

reactions generally observed in the reaction of epoxidised polyisoprene with acids¹⁹

TABLE 2 MODIFICATION YIELDS (X%) IN THE REACTION OF 27% EPOXIDISED LIQUID NATURAL RUBBER WITH DIACIDS OR ANHYDRIDES CATALYSED BY THE TETRABUTYLAMMONIUM SALT OF THE DIACIDS, IN CHLOROFORM AT 70°C

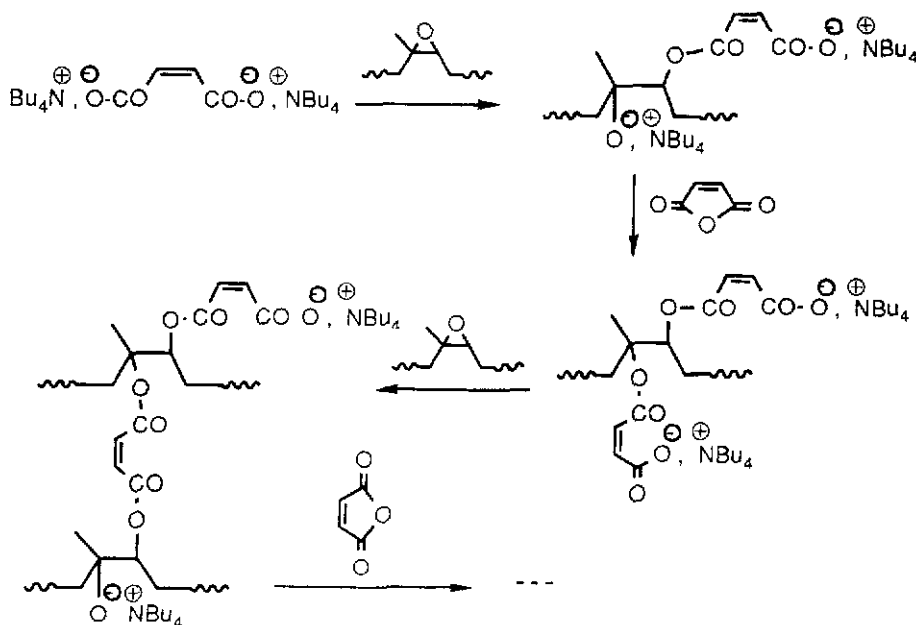
Anhydride or diacid ^d	X%			Gelation
	8h	24 h	72 h	
Maleic anhydride	12.1	20.5	23.1	+
Malonic acid	11.4	18.7	23.0	-
Succinic anhydride	9.6	15.4	17.4	+
Succinic acid	0.7	3.8	4.3	-
Glutaric anhydride	4.1	16.9	19.2	+
Glutaric acid	0.3	2.6	3.3	-
Phthalic anhydride	6.8	10.2	15.4	+

^d [epoxide] = [diacid or anhydride] = 0.05 mol/litre, [catalyst] = 5 mmol/litre

+ gelification

- no gelification (observation at 72 h)

Maleic anhydride has been used as the crosslinking agent for the preparation of polymeric particles (Scheme 2).

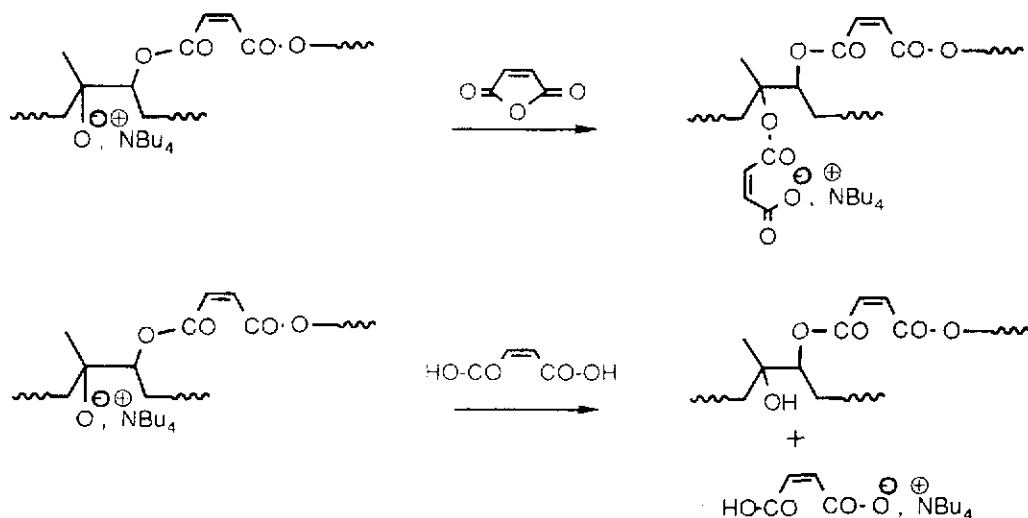


Scheme 2

Crosslinking of epoxidised 1,4-polyisoprene by the anhydride proceeds probably by the preliminary addition of tetrabutylammonium maleate on the oxirane followed by attack of the anhydride by the formed alcoholate, as it has been already proposed^{20,21} for the

in the aqueous phase containing a non-ionic emulsifier (Tween 20) under stirring

- elimination of chloroform by warming slowly (4 h), up to 70°C.



Scheme 3

synthesis of polyesters. This is corroborated by the fact that with malonic acid, gelation is not observed at the same reaction yield as for maleic anhydride: exchange of the ammonium group does not involve bond creation with the polymer in the case of diacids (*Scheme 3*).

Diacids are needed to obtain a larger modification yield before gelation is observed.

Crosslinked 1,4-polyisoprene Containing Free NAA

The first trials for the preparation of crosslinked particles from epoxidised polyisoprene without NAA did not give the expected result: the reaction yield was too low and aggregation of the particles was observed when isolated. The operating process involved three steps:

- dispersion of the polymer solution in chloroform containing maleic anhydride

- isolation of the particles after 19 h of reaction at 70°C.

In order to favour the crosslinking and to avoid diffusion of the reagents in the emulsion medium, an important modification in the process was a preliminary step consisting of warming the polymer and anhydride solution at 70°C for 1 h in the presence of the catalyst. A partial reaction of the anhydride was obtained but gelation was not observed. Emulsion was then carried out at 70°C by dropping the solution in the aqueous phase with stirring. The reaction was carried out at 70°C for 23 h before isolating the particles.

Preparation of particles containing NAA was then studied. The quantity of NAA in the particles (*Table 3*, expressed in milligramme of NAA per gramme of product) was determined by UV spectroscopy after extraction by refluxing ethanol for 16 h.

TABLE 3. RESULTS OF ENCAPSULATION OF NAA BY 27% EPOXIDISED LIQUID NATURAL RUBBER CROSSLINKED BY MALEIC ANHYDRIDE

Method of preparation ^a	ANA ^b	Initial quantity/g of polymer		
		NAA(mg)	CHCl ₃ (ml)	H ₂ O(ml)
NAA in the aqueous phase	19-26	190	41	103
NAA in the aqueous phase	31-35	960	41	103
NAA IN THE aqueous phase, pH = 3.5	37	960	41	103
NAA in CHCl ₃	47	960	41	103
Impregnation	245	1000	20	—
Impregnation	328	1000	18	—

^a [epoxide] = [anhydride], [catalyst] = 5 mmol/litre^b Milligramme NAA encapsulated per gramme of product

When NAA is initially introduced in the aqueous phase, it is distributed preferentially in this phase when the emulsion is formed as shown by the low content of NAA in the particles.

Acidification of the aqueous phase decreases the solubility of NAA, and this resulted in a slight augmentation of NAA content in the particles.

Introduction of NAA in the chloroform solution resulted in a slight improvement compared to the former method. However the encapsulated NAA level remains low (*Table 3*). Washing during recovery of the particles explains part of this result (1% of initial NAA in the aqueous phase after the first washing of particles).

In order to improve encapsulation, impregnation of preformed crosslinked particles was performed by a chloroform solution of NAA. NAA content over 0.3 g/g of product was obtained. This yield is the function of the NAA concentration in chloroform.

Crosslinked 1,4-polyisoprene Containing Free and Linked NAA

Epoxidised polyisoprene modified by NAA can also be further crosslinked by using unreacted oxirane groups after the first modifi-

cation step, leading to polyisoprene containing linked NAA. Particles containing free and linked NAA can be prepared by this method.

The reaction has been performed as in the third example of *Table 3* (NAA in the aqueous phase at acidic pH). With epoxidised and modified¹⁸ synthetic 1,4-polyisoprene, free and linked NAA contents of 73 mg/g and 92 mg/g of particles were obtained (43 mg/g and 126 mg/g respectively with liquid natural rubber).

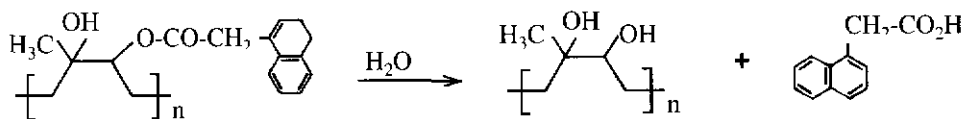
STUDY OF NAA RELEASE FROM THE DIFFERENT FORMS OBTAINED

The study deals with the two polymeric forms containing NAA:

- NAA linked to the polymer (and its corresponding model molecule)
- Particles of crosslinked polyisoprene containing free and linked NAA.

Hydrolysis of 1,4-polyisoprene Modified by NAA

Hydrolysis of 5-hydroxy-5-methyl-4-octyl naphthylacetate (NAA-MO), of NAA-EPIP and NAA-ELNR was carried out in buffer solutions (pH = 4, 6, 7, 8 and 10) for ten days at 25°C, as shown in *Scheme 4*.



Scheme 4

The modified polymer is not soluble in water and this study was done with the polymer powder dispersed by stirring in the buffer solution. Agglomeration of the polymer led sometimes to incoherent results.

The quantity of released NAA is evaluated by UV spectrophotometry at 282 nm, on aliquots every 48 h (Table 4).

The quantities used for hydrolysis studies correspond to about 35–50 mg NAA released in 100 ml of water in the case of total hydrolysis and problems of solubility can arise (solubility of NAA: 0.35 g/litre at pH 4, 0.63 g/litre at pH 6). However, the quantities actually released during the study are never above the limits of solubility of NAA.

In the case of the model molecule (Figure 1), the initial value at $t = 0$ (in fact about 3 min after beginning the mixing of reagents) is too high and seems to correspond to the solubility of NAA-MO in water. If one subtracts this initial value, the quantities released at pH 4 can be considered as negligible.

Release of NAA is favoured in basic media. With the model molecule, the rate of acid release is higher than with polymers: 9.2% at pH 10 after ten days against 2.8% and 5.2% respectively for NAA-PIP and NAA-LNR (Figure 2). This can be explained by a better accessibility of the ester groups in the first case. These yields are low but stimulators are generally efficient at low concentrations. It should be interesting to get higher epoxidation yields and NAA content in the polymer. The hydrophilic character of the polymer would be enhanced by the OH groups introduced during modification and the rate of hydrolysis would be improved at the same time.

Release of NAA from Crosslinked Polyisoprene Particles

Release of NAA from 1,4-polyisoprene was studied on particles containing free or free as well as linked NAA. The initial rate is rapid but a value quasi-constant is observed after four days (Figure 3).

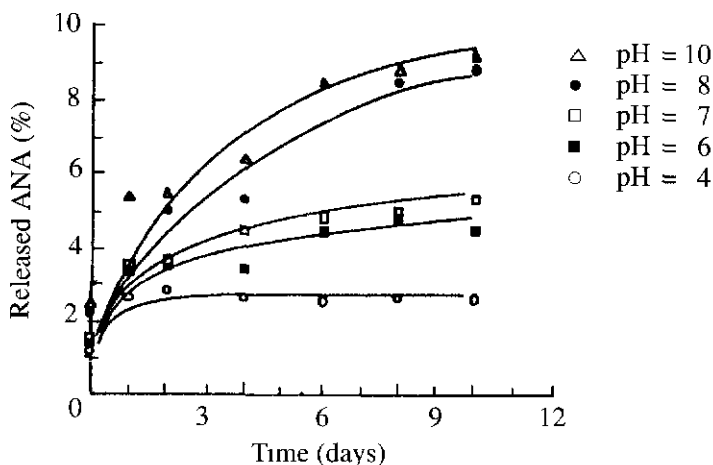


Figure 1 Hydrolysis of NAA-MO in buffer solutions at 25°C [NAA-MO] = 0.8 g/litre

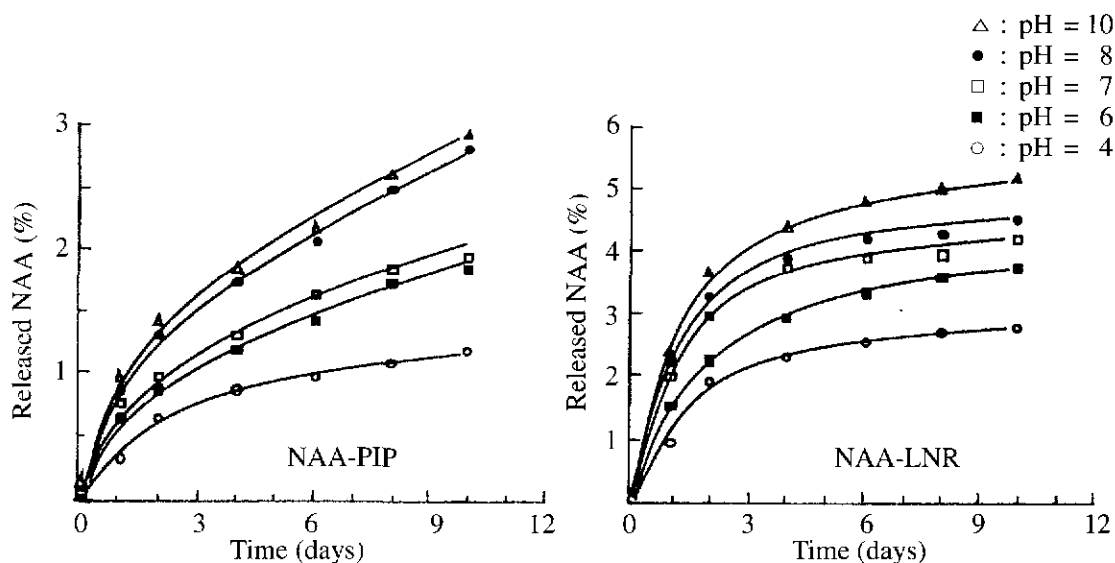


Figure 2. Hydrolysis of polymeric derivatives of NAA in buffer solutions at 25°C [polymer] = 4g/litre, NAA initial content: NAA-PIP: 37‰; NAA-LNR: 33‰.

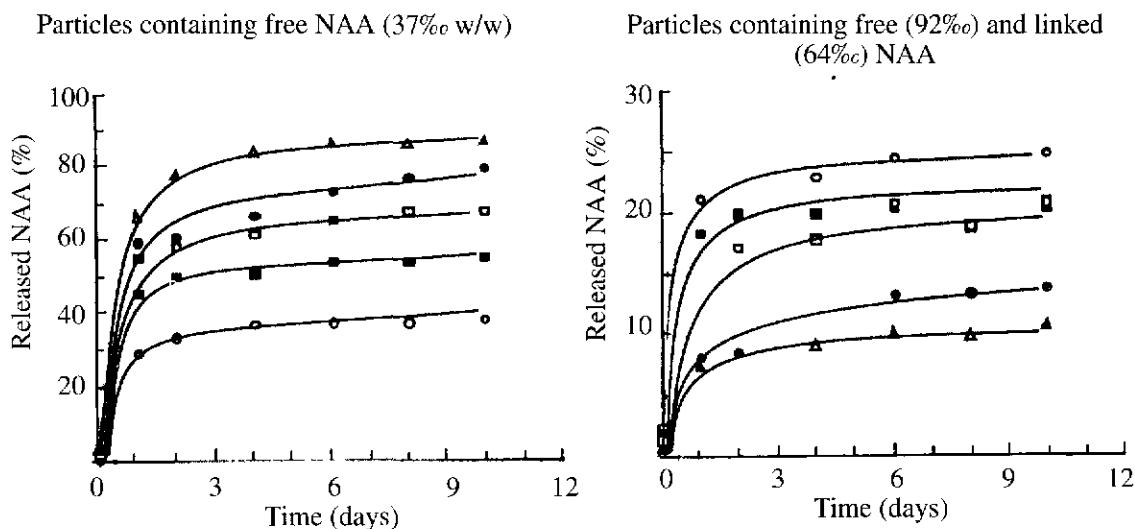


Figure 3. Release of NAA from 1,4-polyisoprene particles in buffer solutions at 25°C. [particles] = 2 g/litre

Release is favoured by increase of pH and solubility of NAA with pH plays undoubtedly a significant role.

It seems surprising that the rate of release is higher in the case of particles containing only

free NAA although the initial content is lower. In fact, this effect is due to the representation in percentage of the total quantity of NAA in the particle. The ponderal quantity is effectively higher for particles containing more free NAA.

With particles obtained from liquid natural rubber, comparable results were obtained but the observed maximum was always slightly higher than that obtained from synthetic polyisoprene. This difference can be explained by a difference of granulometry between the two types of particles. Those obtained with LNR are finer and accessibility of water inside the particle is thus favoured.

NAA LNR has been evaluated at IRCA/CIRAD (Bimbresso - Côte d'Ivoire) for latex stimulation on *Hevea* trees (Table 4). The modified polymer diluted in palm oil was applied on the tree in the same way as for Ethrel or free NAA. These preliminary results are very encouraging as one can see that bonding of NAA to a polymeric carrier does not inhibit its activity. The modified polymer is even more efficient than free acid one month after treatment.

TABLE 4 RESULTS OF *HEVEA* STIMULATION BY ETHREL, NAA AND ELNR MODIFIED

Stimulation by	Latex production ^d (g/tree/tapping)
Ethrel ^a	84.4
ANA ^b	74.5
NAA LNR ^c	78.4
(Unstimulated)	44.1

^a 2.5% w/w in palm oil

^b 5% w/w in carboxymethyl cellulose

^c 5% w/w of NAA equivalent in palm oil

^d In gramme of dry extract

CONCLUSION

A polymeric support of free or linked naphthylacetic acid (a stimulator for the production of latex by *Hevea*), can be obtained from epoxidised synthetic 1,4-polyisoprene or liquid natural rubber.

Crosslinking of epoxidised polymers by diacids or anhydrides catalysed by the tetrabutylammonium salt of the corresponding diacids was performed in emulsion. With maleic anhydride, polymeric particles containing free NAA were prepared with a 30% and 40% weight content of NAA.

Particles containing free and linked NAA were also prepared from modified polymers. The low content of free NAA is due to its solubility in water during emulsion preparation and washing of the particles.

Impregnation of preformed particles is a means to obtain particles containing a more significant quantity of NAA.

Hydrolysis, in heterogeneous phase in buffer solutions, of NAA derivatives of a model molecule (4,5-epoxy-4-methyloctane), epoxidised 1,4-polyisoprene and liquid natural rubber shows that it is favoured in basic media.

This particular formulation leads to a high initial rate of liberation, which should be modulable by changing the physico-chemical properties of the polymer (molecular weight, epoxidation yield, epoxide modification extent and crosslinking density). A 'composite' formulation, with coating of the particles containing free NAA by polymer having linked acid, could also be envisaged.

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