1.ANS/ACS international meeting on radiation processing.Porto Rico,9-13 May 1976
CEA-CONF--3696
FR7701410

SYNTHESIS OF COPOLYMERS SUITABLE FOR THE STORAGE AND SLOW RELEASE OF REACTANTS

CASES OF COPPER SALTS FOR INTRA-UTERINE DEVICES

by Gilbert GAUSSENS and Jeanne DUCHEMIN-BERTHET
Commissariat à l'Energie Atomique/CAPRI (France)

This research has been carried out to determine whether a grafted poly(ethylene-vinyl acetate) matrix could be prepared which would release useful amounts of copper salts when used in intra-uterine devices.

Intra-uterine devices were prepared by grafting hydroxyethyl acrylate onto ethylene-vinylacetate copolymers (EVA).

The kinetics of the grafting reaction were studied. The grafting reaction was initiated by cobalt 60 gamma rays usingthe simultaneous method.

The conditions of copper salts absorption by the grafted copolymers were selected.

The average quantity of copper salts released daily from the intra-uterine device was measured as a function of grafting rati and the amount of copper salt initially incorporated in the grafted polymeric matrix.

In vitro experiments samples showed constant release rates during a period of 18 months.

1st INTERNATIONAL MEETING ON RADIATION PROCESSING

SYNTHESIS OF COPOLYMERS SUITABLE FOR THE STORAGE AND SLOW RELEASE OF REACTANTS

CASES OF COPPER SALTS FOR INTRA-UTERINE DEVICES

by Gilbert GAUSSENS and Jeanne DUCHEMIN-BERTHET
Commissariat à l'Energie Atomique/CAPRI (France)

1. INTRODUCTION

Research on the synthesis of copolymers suitable for the storage and slow release of copper salts were carried out with a commercial ethylene - vinyl acetate copolymer (EVA). The hydrophobic copolymer was grafted under cobalt sixty gamma rays by the simultaneous method with hydrophilic monomers such as hydroxy ethyl acrylate. Such radiation graft copolymerization is a useful technique to graft hydrogels to polymer supports (1,2,3).

The hydrophilic grafted copolymer made can be expanded by aqueous solution (4) and the release rate is observed to be constant over a long period of experimentation. Intra uterine devices were also made with this type of copolymer.

Various attempts to impregnate devices like the T intra-uterine device with metallic copper (5) or copper salts such as copper carbonate or copper sulfate have been described in the literature. But these have thus far not been successful because the copper is not release from polyethylene and therefore has no effect.

2. MODE OF ACTION

The contraceptive effect of copper apparently results from the release of copper ions into the uterine cavity where they influence various biologicals reactions. These reactions are limited to local changes in the intra-uterine environment and little or no copper is found elsewhere in the organism (6).

../...

With IUD's containing copper wire, HAGENFELDT determined that during the first year, the average daily release of copper was about 45 micrograms (7). The rate of release of copper, with copper wire twisted around the plastic intra-uterine devices, however, decreased as a function of time.

GIBOR and his co-workers (6,8) estimated that immediately after insertion, a single copper seven device released on the averag 55.5 micrograms of copper per day, but after 12 months, the device released 33 micrograms per day, and at 18 eighteen months, only 11.6 micrograms per day.

In-vitro experiments have shown, however, that with the grafted EVA copolymer IUD the release rate of the absorbed copper salt is more constant over the eighteen month period. In this paper we will present data from preliminary experiments.

3. MATERIALS AND METHODS

Grafting under cobalt sixty gamma rays was carried out in the following conditions : intra-uterine devices (IUD) made with ethylene vinylacetate copolymers by injection were introduced into glass tubes containing a monomer solution, and then degassed twice by a vacuum line. Copper acetate (2%) was introduced in the solution to inhibit the homopolymerization of the monomer.

The sealed tubes were heated to 40°C in a thermostatic bath and irradiated in this condition. After irradiation, the grafted IUD samples were washed in distilled water for two hours at room temperature and then dried at sixty degrees centigrade to determine the graft copolymer weight. Afterwards, the grafted IUD's were soaked in a concentrated copper nitrate solution at 60°C. The amount of copper salt stored in the IUD's was then determined as a function of time by weighing the samples.

4. EXPERIMENTAL RESULTS

4.1. Effect of dose on the grafting ratio and crosslinking

The samples were irradiated in a hydroxy ethyl acrylate (HEA) and polyethylene glycol diacrylate (PEGDIA) solution with a polyfunctional monomer-vinyl monomer ratio of 1/4. The dose rate was 0.2 Mrad/hour.

.../...

The grafting ratio as a function of dose is shown on the Figure 1. It can be seen that grafting ratio increases with increasing dose. Probably, the reaction kinetics are controlled by the diffusion of the monomers in the EVA copolymer. We observe that 21% of the grafting is obtained at 3.4 Mrad dose.

4.2. Effect of the polyfunctional monomer vinyl monomer ratio ($\frac{PFM}{M}$)

The grafting kinetics are a function of the polyfunctional monomer-vinyl monomer ratio and also of the chemical type of the polyunsaturated monomers, for example : Diethylene glycol diacrylate (DIEGDIA) and tetraethylene glycol diacrylate (TEGDIA).

A plot of grafting ratio versus dose is shown in Figure 2. It is apparent that, for a given dose, the grafting ratio is higher with diethylene glycol diacrylate than with tetraethylene glycol diacrylate. With these two polyunsaturated monomers, the grafting ratio is influenced very little by the polyfunctional monomer-vinyl monomer ratio, in the limit of our experiments.

4.3. Effect of dose rate

Dose rate is an important parameter in the grafting kinetics which can be taken into account. The percent of grafting is plotted against the dose for various dose rates in Figure 3.

As expected, for a given dose the grafting ratio decreases with the increasing dose rate. A high grafting ratio equal to 50% however, can be reached for a radiation dose of 1.8 Mrad and a dose rate of 0.045 Mrad/hour in the aqueous hydroxy ethyl acrylate solution without a polyunsaturated monomer. If we compare this grafting ratio to that obtained in a solution containing a poly-monomer under the same irradiation conditions (see Figure 2), it is apparent that the addition of a polyfunctional monomer decreases the grafting level. These data suggest that when the hydrogel region is becoming cross-linked, the diffusion rate of hydroxyethyl acrylate slows down.

These factors influence the structure of the grafted polymer, and subsequently affect the absorption characteristics. Indeed, the amount of copper salt which can be absorbed in the grafted IUD is a function of the grafting ratio, and increases with the percent of polyhydroxy ethyl acrylate grafting.

.../...

4.4. Copper salt absorbance of the grafted IUD

The amount of copper salt which can be included in the crosslinked hydrophilic enclosure of the grafted IUD is a function of the grafting ratio and also of the polyinsaturated monomer concentration of the aqueous solution. Figure 4 shows the curves of copper salt amount absorbed as a function of the time of soaking. The grafting ratio is approximately the same (21% and 22.6% for two different polyfunctional monomers, vinyl monomer ratio 1/4, and 1/(2.3). The polyfunctional monomer is polyethylene glycol diacr late (PEGDIA) while the vinyl monomer is hydroxylethyl acrylate (HEA

The dose rate was 0.135 Mrad/hour. Note that a surprising effect is observed : a higher absorbance ratio of copper salt is obtained with the monomer solution in which the polyethylene glycol diacrylate is more concentrated.

The amount of copper salt incorporated in the grafted polymeric matrix reachs a plateau value of 25% for $\frac{\text{PEGDIA}}{\text{HEA}} = 1/(2.3)$. and 20% for $\frac{\text{PEGDIA}}{\text{HEA}} = 1/4$.

This amount corresponds, respectively to 31 and 29 milligrams of copper in each IUD.

The effect of time on percent copper salt absorption is shown in Figure 5 for a HEA monomer grafted without polyunsaturated monomer at a grafting level of 22.6%.

It can be seen that only 10% of the copper salt is absorbed by the grafted EVA copolymer. It is apparent that addition of PEGDIA permits attainment of much higher copper levels either as the polyunsaturated monomer increases or as time of soaking increases.

Examination of Figure 6 shows that copper salt absorption in a grafted polymeric matrix, for a given grafting ratio (21%), is a function of dose rate.

Increasing the dose rate leads to a marked increase of copper salt content in grafted IUD's for a polyethylene glycol diacr late-hydroxyethyl acrylate ratio equal to 1/4, which suggests that the structure of the crosslinked hydrophilic regions are modified by the effect of dose.

.../...

For a higher PEGDIA - HEA ratio (1/2.3), however, the effect of dose rate on the absorption of copper salt is almost negli geable, as shown by the curves in Figure 7. These effects of dose rate are not yet fully explained.

5. RELEASE RATE OF THE COPPER SALT

In-vitro experiments have been carried out in a continuous flow system that was maintained at 37°C and used for the "in-vitro" release investigation. An isotonic media of 0.9% sodium chloride solution was passed through the glass system containing the grafted IUD at a rate of 400 ml per 24 hours. The eluant solution was remove periodically for determination of copper content by an UV spectro-photometric method utilizing a copper-dithizone complex.

The average amount of copper salt released daily from the intra uterine device was measured as a function of the grafting rati and the amount of copper salt initially incorporated in the grafted polymeric matrix.

Figure 8 and 9 show the release rate of copper nitrate in an "in-vitro" experiment performed at 37°C, for a grafted IUD (21.8%) containing 14.25 milligrams of copper. It can be seen that the copper release rate decreases very slowly during 2 months and reaches, within the limit of experimental error, a constant value of 20 micrograms per day during the following 16 months. A plot of copper amount released against time is shown in Figure 10, for in-vitro experiments which were carried out at 45°C. The release rate decreases more rapidly than at 37°C during the first month, while for the following 16 months the rate is stabilized at 30 micrograms per day. We can conclude that the release rate of copper salt increa ses with the increasing temperature.

CONCLUSION

Poly hydroxyethylacrylate hydrogels have been covalently bonded onto ethylene vinyl acetate copolymers using a radiation - grafting technique. The critical parameters controlling the copper salt amount absorbed and the release rate are the grafting solution composition, absorbed radiation dose and dose rate.

.../...

Present in-vitro experiments involving IUD's showed constant release rates during a period of 18 months and we expect t: increase this to 2 years.

This study is being continued on a pilot scale.

.../...

ACKNOWLEDGMENT

The intra uterine devices were graciously supplied by Dr. COURNUT and Dr PIVAUDRAN of SODERMEC Company.

REFERENCES

(1) HOFFMAN A.S. and al.
Trans. Amer. Soc. Artif. Inter Organs 14,82 (1968).

(2) RATNER B.D. and HOFFMAN A.S.
J. Appl. Polymer Sci. 18 3183 (1974).

(3) HOFFMAN A.S. and al.
In "Permeability of plastic films and coatings"
ed. H.B. Hopfenberg - Plenum press - N.Y. 1974 p. 441.

(4) LEVOWITZ B.P. and al.
Trans. Amer. Soc. Artif. Inter. Organs. 14, 82, 1482 (1968).

(5) TATUM H.J.
Contraception with the endonterine copper T : a preliminary report in : Sobrero A.J. and Harvey R.M. Eds. Advances in planned parenthood Vol 7 Amsterdam, Excerpta Medica, 1972 p. 92-99.

(6) Les dispositifs intra-uterins
Bulletin serie B n° 1 Mai 1974
Department of Medical and Public affairs, the George Washington University Medical Center - Washington.

(7) HAGENFELDT K.
Intrauterine contraception with the copper T device
Contraception 6 (1) 37-54 (1972).

(8) GIBORY. NISSEN C.H. and BRUNSFELD M.
Report to investigators on the Cu-7 intrauterine device - A summary of the data submitted to FDA in the new drug application of December 1972.

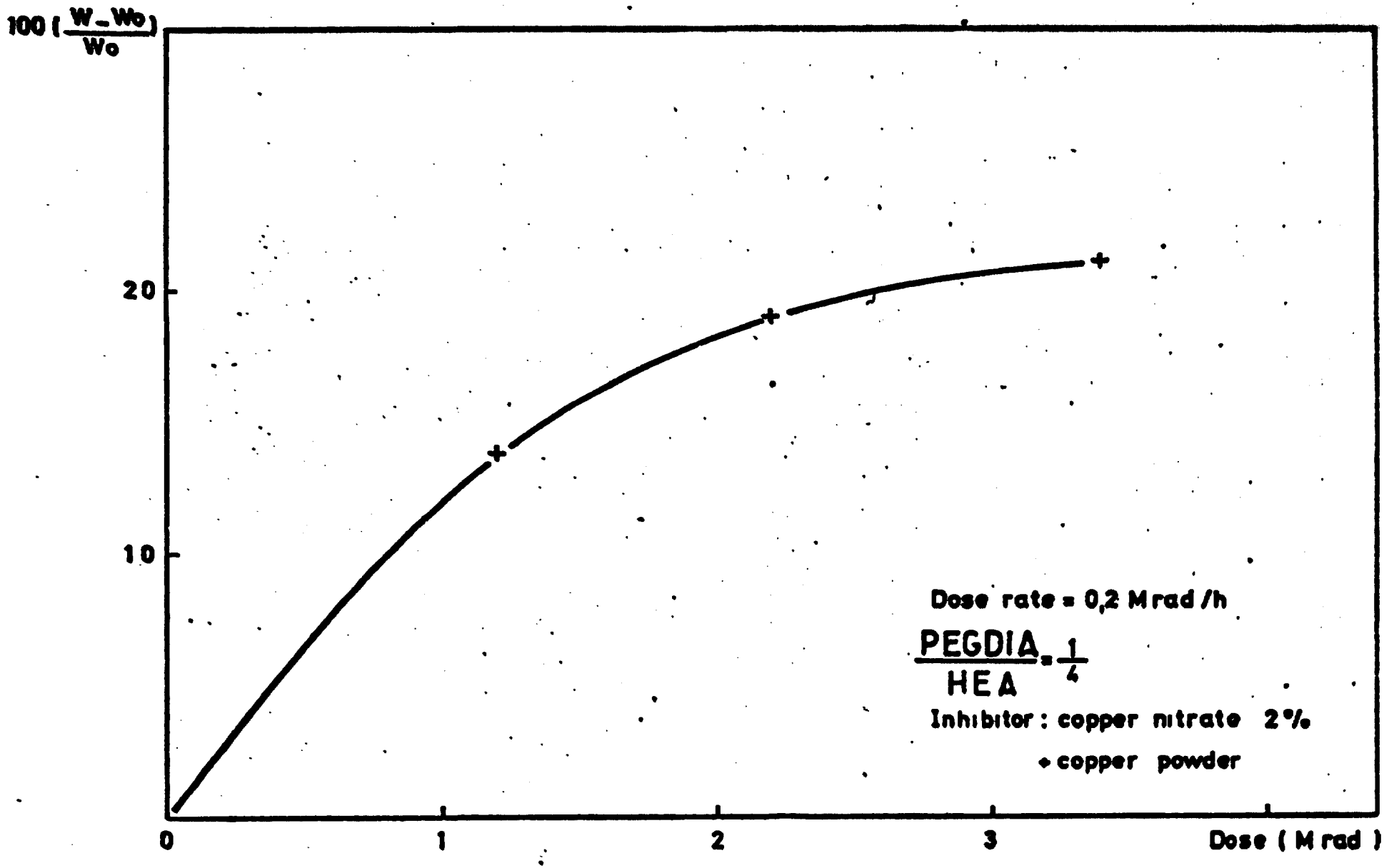

Fig.1 Influence of the dose on the rate of grafting and crosslinking hydroxy ethyl acrylate and polyethylene glycol diacrylate onto EVA copolymer IUD with cobalt 60 gamma rays irradiation

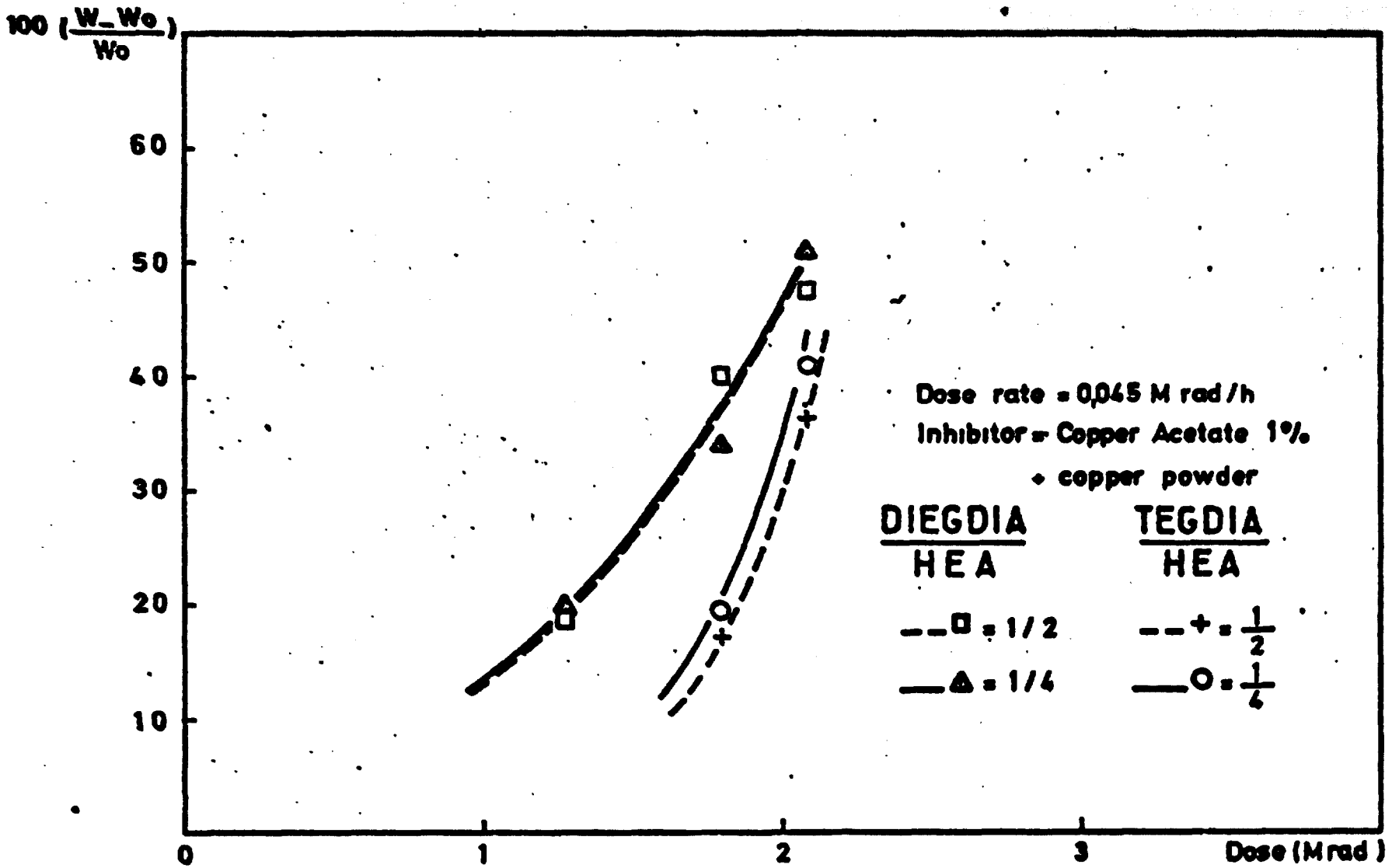

Fig. 2 Influence of the dose on the rate of grafting and crosslinking onto EVA copolymer IUD with cobalt 60 gamma rays irradiation for different $\frac{PFM}{HEA}$ ratios

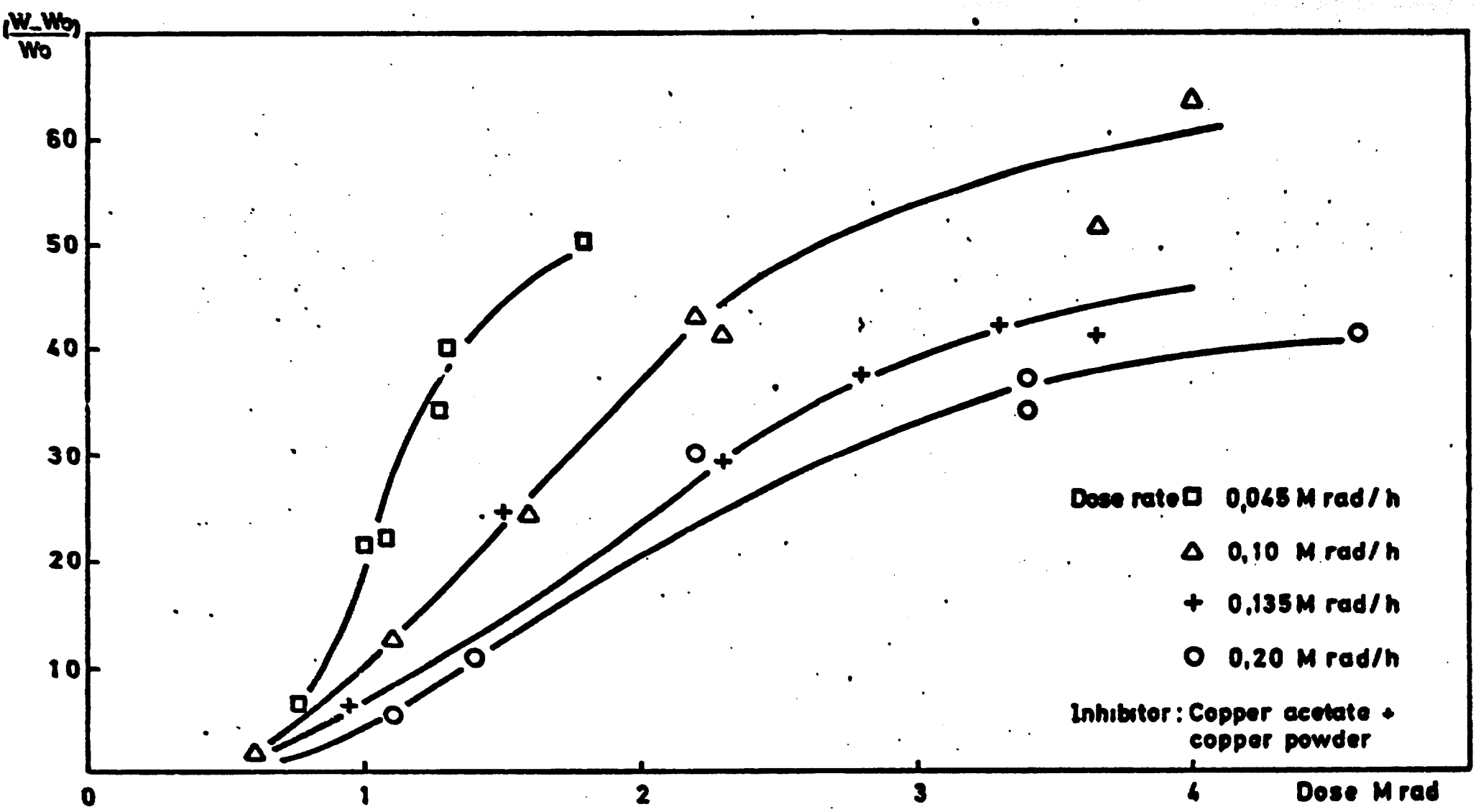

Fig. 3 Influence of the dose on the rate of direct grafting of hydroxy ethyl acrylate onto EVA copolymere IUD with cobalt 60 gamma rays irradiation at different dose rates

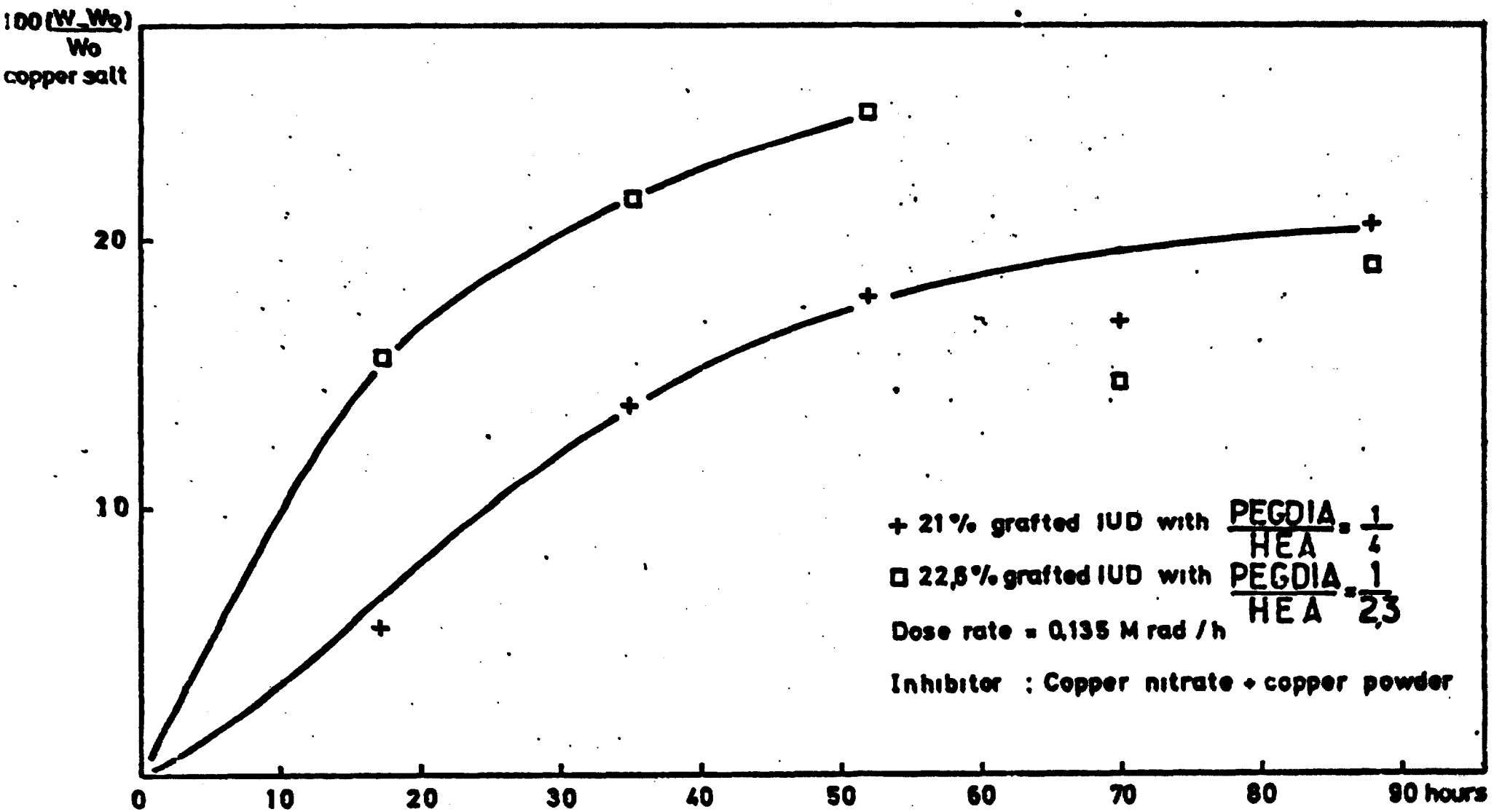

Fig. 4 Copper salt amount in grafted-crosslinked IUD as a function of immersion time. Influence of the $\frac{PEGDIA}{HEA}$ ratio

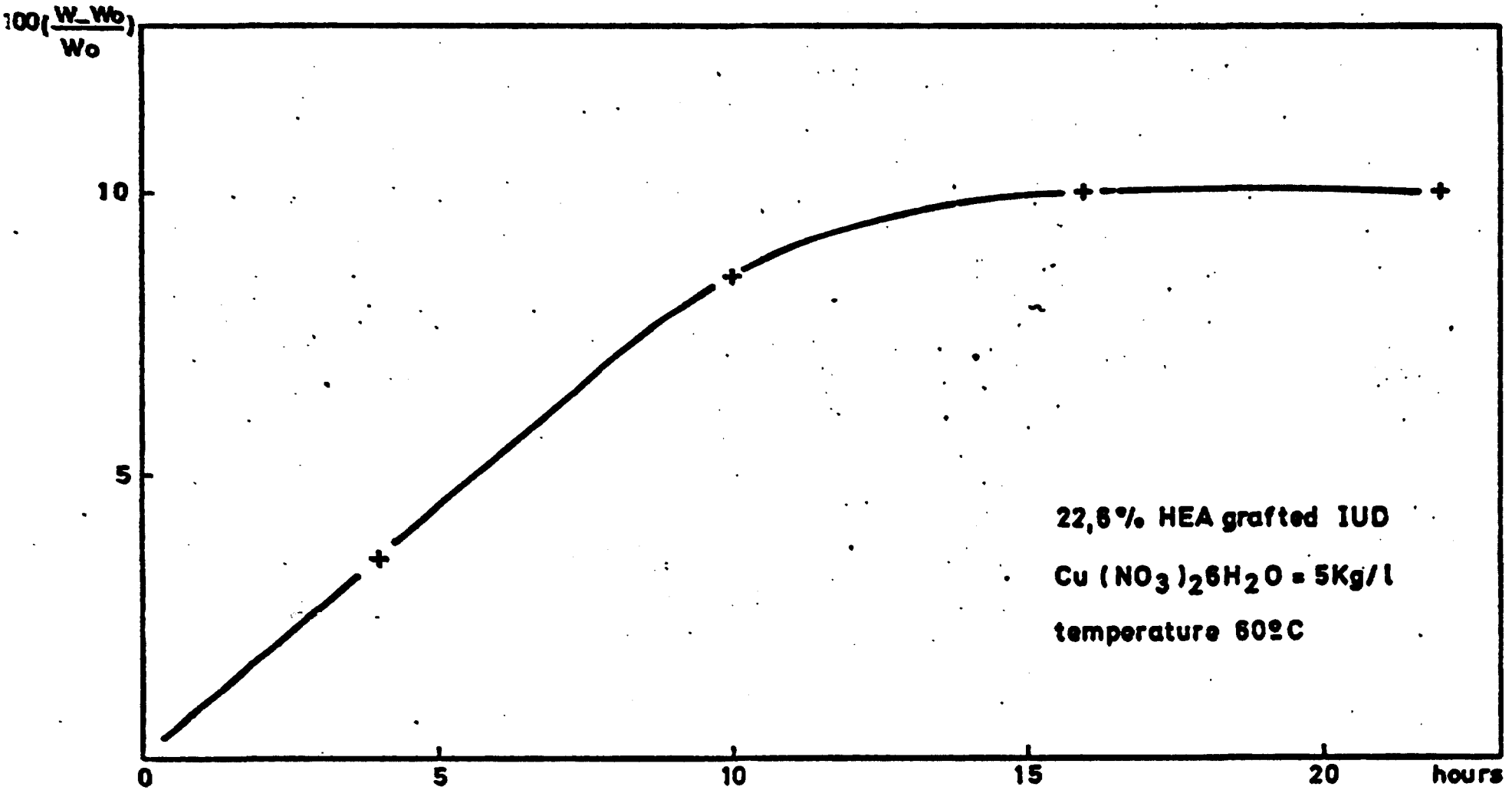

Fig. 5 Copper salt amount in HEA grafted IUD as a function of immersion time

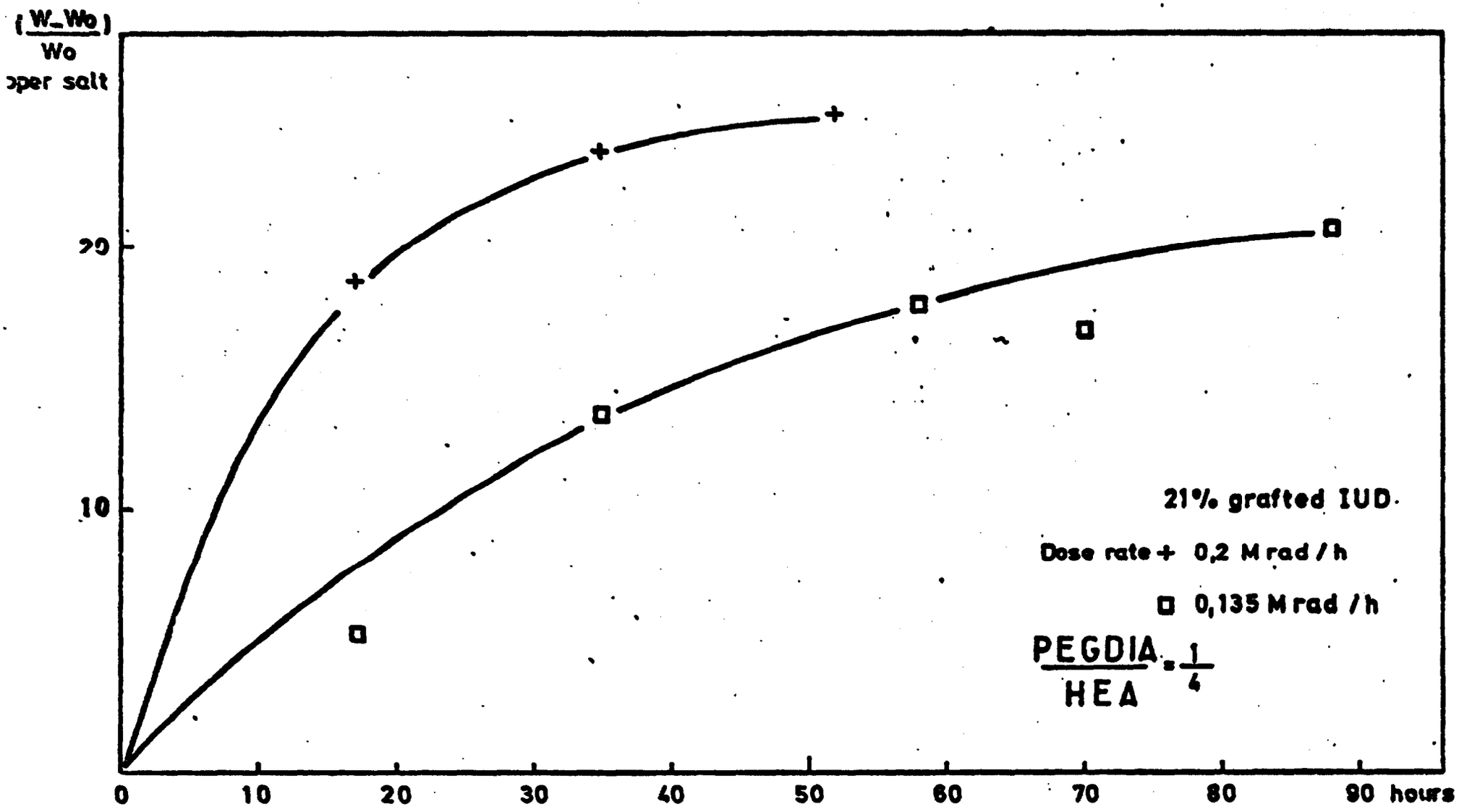

Fig. 6 Copper salt amount in grafted crosslinked IUD as a function of immersion time. Influence of the dose rate

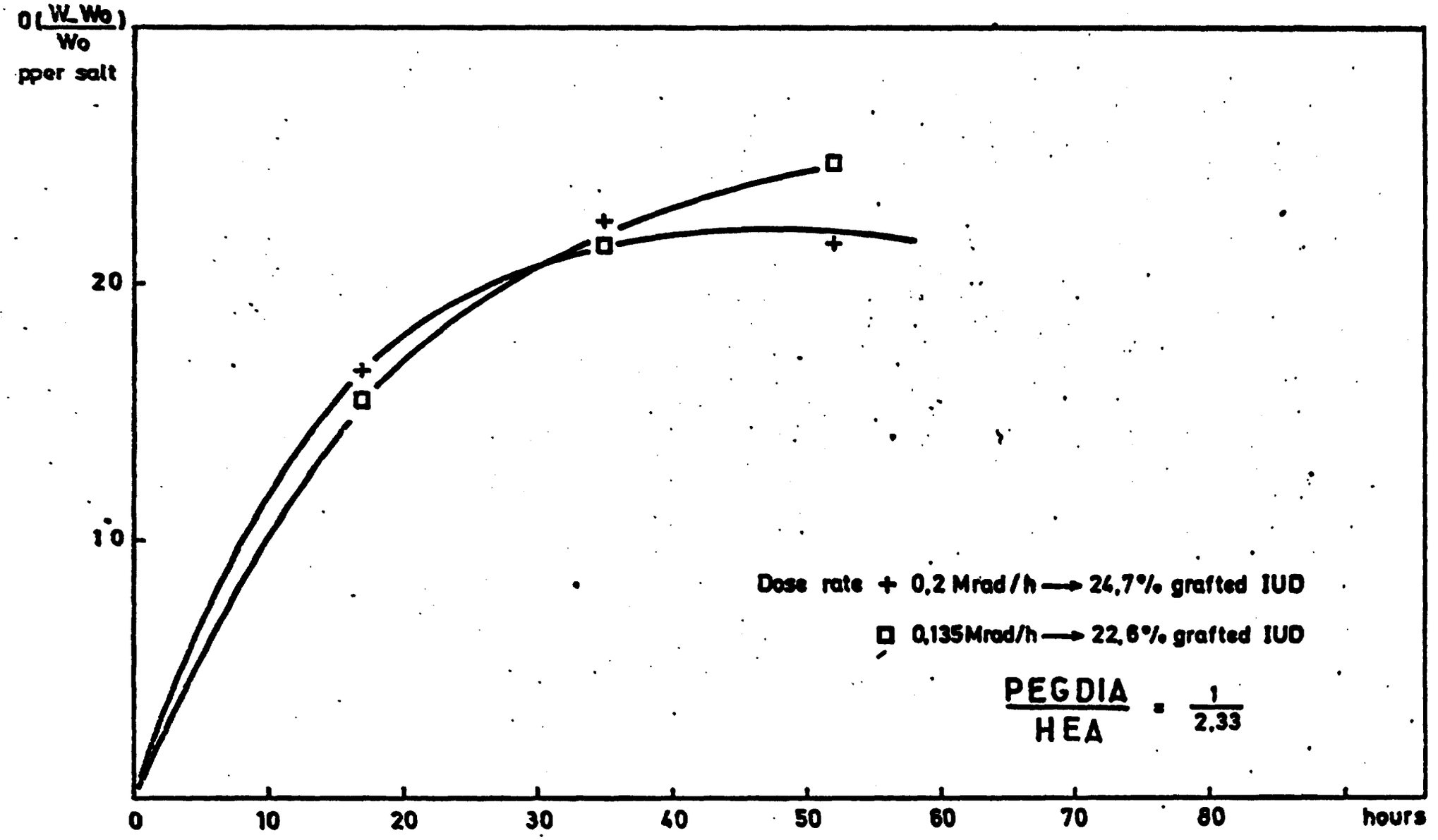

Fig: 7. Copper salt amount in grafted crosslinked IUD as a function of immersion time_Influence of the dose rate

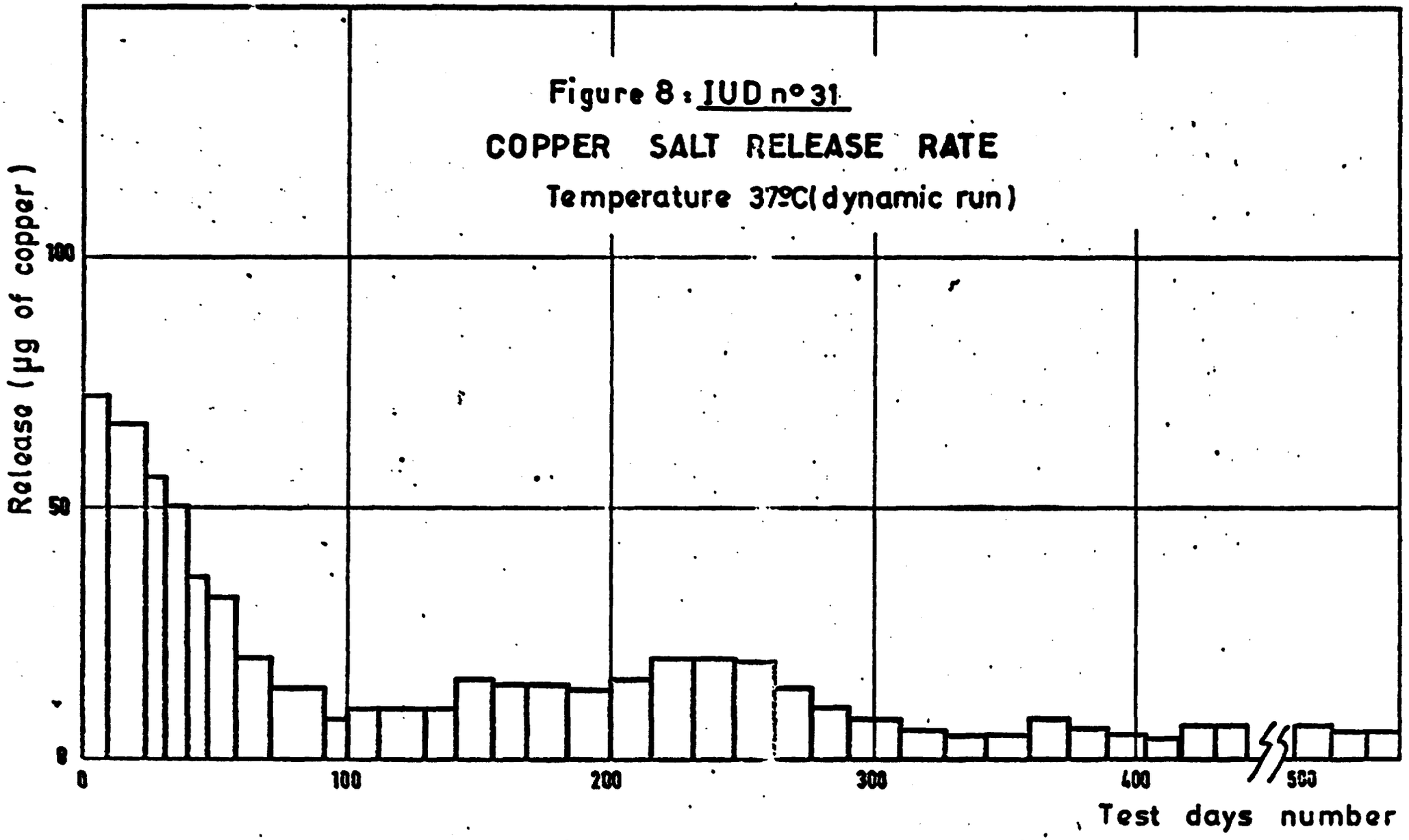
Figure 8 : IUD n° 31
COPPER SALT RELEASE RATE
Temperature 37°C (dynamic run)
Release (µg of copper)
100
50
0
0
100
200
300
400
500
Test days number

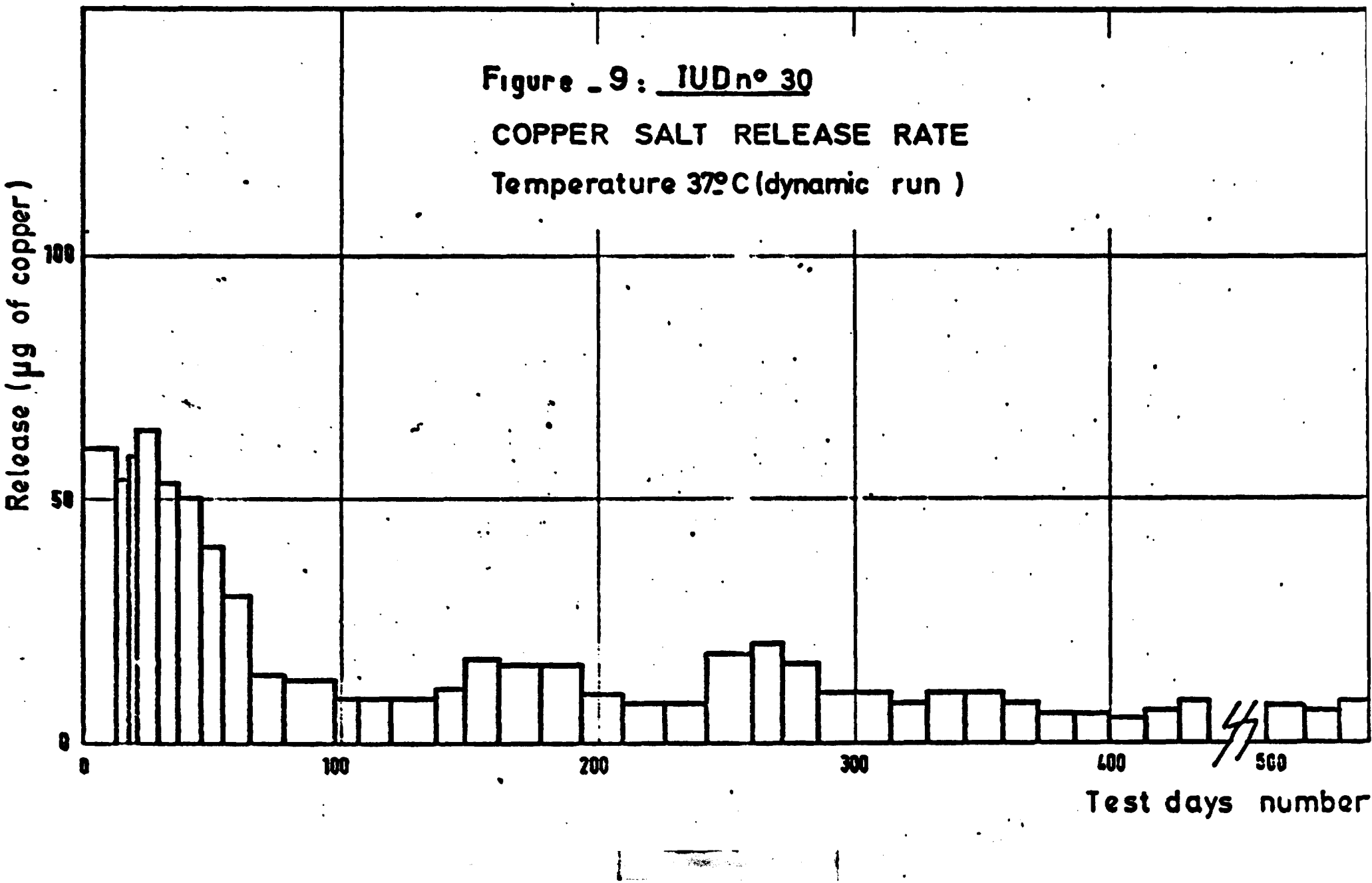
Figure _ 9 : IUD n° 30
COPPER SALT RELEASE RATE
Temperature 37° C (dynamic run)
Release (µg of copper)
100
50
0
0
100
200
300
400
500
Test days number

Figure: 10 - IUD n°30

COPPER SALT RELEASE RATE

Temperature 45°C (dynamic run)