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SYNTHESES AND TOXICITY OF MONOMERS AND POLYMERS CONTAINING 5-FLUOROURACIL

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ABSTRACT

The monomers 1-(2-carbomethoxyacryloyl)-5-fluorouracil (CMAFU) and 1-(methacryloyloxyethyl)-5-fluorouracil (MAOEFU) were synthesized from 2,4-bis(trimethylsilyloxy)-5-fluoropyrimidine (BTMSF). Poly(MAOEFU) was obtained by radical polymerization with 2,2′-azobisisobutyronitrile (AIBN) in cyclohexanone at 60°C. Copolymerizations of CMAFU or MAOEFU with methyl methacrylate (MMA) or styrene (St) were carried out with AIBN at 60°C. The copolymer compositions were analyzed by infrared (IR) spectroscopy for poly(CMAFU-*co*-St) and poly(CMAFU-*co*-MMA), or by ultraviolet (UV) spectroscopy for poly(MAOEFU-*co*-MMA), respectively. The monomer reactivity ratios r_1 and r_2 were determined by the Kelen–Tüdös method: r_1 (CMAFU) = 0.01 and r_2 (St) = 7.46; r_1 (CMAFU) = 0.01 and r_2 (MMA) = 35.08; r_1 (MAOEFU) = 0.77 and r_2 (MMA) = 1.13. These values imply that the copolymerizations were significantly affected by the steric hindrances of monomers containing 5-fluorouracil (5-FU). Toxicity of the monomers and polymers synthesized against *Drosophila melanogaster* was investigated by the adult feeding method of Lewis and

poly(CMAFU-*co*-St) > poly(CMAFU-*co*-MMA) > CMAFU > control and 5-FU > poly(MAOEFU-*co*-MMA) > MAOEFU > poly(MAOEFU) > control.

INTRODUCTION

The inhibitory properties of 5-fluorouracil (5-FU) for tumor growth and its use in cancer chemotherapy have resulted in extensive work on related compounds. It was observed, however, that 5-FU has strong side effects such as gastrointestinal toxicity and delivery problems [1, 2]. Many attempts have been made to reduce those side effects of 5-FU by synthesizing new polymeric drugs containing 5-FU as part of a polymer backbone and as a pendant group or as a terminal group on the polymer chain [3–6].

Butler et al. synthesized 1-(2-carbomethoxyacryloyl)-5-fluorouracil (CMAFU) and the copolymers of CMAFU with vinyl monomers such as styrene, 2-chloroethyl vinyl ether, and vinyl ether [7]. They reported that those copolymers were active against P388 lymphocytic leukaemia. Ouchi et al. synthesized acryloyl-type polymer fixing 5-FU residues through D-glucofuranoses and investigated its antitumor activity [8]. Akashi et al. reported on the syntheses of *N*-methacryloyloxyethyl-5-fluorouracil (MAOEFU), 1-*N*-acryloyl-5-fluorouracil, 1-*N*-Methacryloyl-5-fluorouracil, and their copolymers [9, 10]. They also found that the antitumor activity per equivalent amount of those polymers was greater than that of free 5-FU alone.

Most research has been directed to reveal the antitumor activity of those polymeric drugs containing 5-FU [7–10], but no work to reveal the toxicity of the polymeric drugs in *Drosophila melanogaster* have been published. According to the biological sciences, the short generation time and prolific breeding characteristics of the vinegar fly *D. melanogaster* have made it very attractive to geneticists. Its convenient characteristics as an experimental organism also include ease of culturing (it can be raising on a variety of single culture media) and its small size (ease in handling and storage) [11, 12].

Even though research on the biological activities of those polymeric drugs are crucially important, information on the reactivities of those potential antitumor monomers is of equal importance.

In this work we deal with the radical homopolymerizations of CMAFU and MAOEFU, and the copolymerizations of these monomers with methyl methacrylate (MMA) and styrene (St). The toxicities of the monomers and polymers synthesized were investigated against *D. melanogaster* by the adult feeding method of Lewis and Bacher [11].

EXPERIMENTAL

Syntheses of Monomers

1-(2-Carbomethoxyacryloyl)-5-fluorouracil (CMAFU)

CMAFU was prepared by reacting 2,4-bis(trimethylsilyloxy)-5-fluoropyrimidine (BTMSF) with trans-β-carbomethoxyacryloyl chloride (CMAC) in acetonitrile, as described by Butler et al. [7]. BTMSF was prepared by the method described in the literature [13]. A solution of 9.56 g (35 mmol) BTMSF and 5.20 g (35 mmol)

CMAC in 150 mL dry acetonitrile was added to a 300-mL round-bottomed flask equipped with a reflux condenser and refluxed for 15 h. After reaction, the solution was allowed to cool to room temperature and the acetonitrile was distilled off under reduced pressure. The residue was further dried under vacuum and redissolved in 50 mL dry acetone. After filtration, the acetone solution was slowly added to 1000 mL *n*-hexane with vigorous stirring, and the precipitate was collected by filtration to yield 6.61 g (78%) CMAFU, mp 148–149°C (lit. 150–151°C [7]).

Analysis. Calculated for $C_9H_7N_2O_5F$ (242.2): C, 44.63; H, 2.91; N, 11.57%. Found: C, 44.47; H, 2.71; N, 11.60%. IR (KBr, cm^{-1}): 3450 (−NH), 3080 (=CH), 2840 (aliphatic C−H), 1725 and 1705 (−C=O), 1250 (−C−O), and 815 (NH). ^{1}H-NMR (acetone-d_6): δ8.2 (d, 6H of pyrimidine ring), 7.8 and 6.7 (d, 2H of ethylenic hydrogen), and 3.7 ppm (s, 3H, $-CH_3$).

1-(2-Methacryloyloxyethyl)-5-fluorouracil (MAOEFU)

MAOEFU was synthesized from 2,4-bis(trimethylsilyloxy)-5-fluoropyrimidine (BTMSF) according to the work of Akashi et al. [9] with slight modification. BTMSF 9.56 g (35 mmol) dissolved in 150 mL dry acetonitrile, 7.72 g (40 mmol) 2-bromoethyl methacrylate, and 0.01 g hydroquinone were placed in a 300-mL three-necked round-bottomed flask equipped with thermometer, reflux condenser, and a magnetic stirring bar. The reaction mixture was stirred at 82°C for 15 days and then cooled to room temperature. After acetonitrile was distilled off under reduced pressure, the mixture was dissolved in 150 mL methanol and filtered. The crude product was purified by recrystallization from water and then dried to a constant weight under vacuum (yield 2.62 g (31%), mp 145–146°C, lit. mp 143–144°C [9]).

Analysis. Calculated for $C_{10}H_{11}N_2O_4F$ (242.2): C, 49.59; H, 4.58; N, 12.57%. Found: C, 49.55; H, 4.52; N, 11.61%. IR (KBr, cm^{-1}): 3040 (=C−H), 2810 (C−H), 1720 (−C=O), 1630 (C=C), and 815 (N−H). ^{1}H-NMR (DMSO-d_6): δ7.9 (d, 6H of pyrimidine ring), 6.1 and 5.7 (s, 2H, $=CH_2$), 4.3 (t, $N-CH_2C$), 3.7 (t, CCH_2O), and 1.7 ppm (s, $-CH_3$).

Syntheses of Polymers

Poly(1-(2-methacryloyloxyethyl)-5-fluorouracil) [poly(MAOEFU)]

A solution of 0.80 g (3.3 mmol) MAOEFU and 0.04 g AIBN in 25 mL dry cyclohexanone was introduced into a dry polymerization tube. The solution was degassed twice by purging with purified N_2 gas. The tube was sealed and placed in a regulated thermostat with a precision of ±0.05°C at 60°C for specified periods. The polymer solution obtained was precipitated in excess *n*-hexane. The precipitate was collected by filtration and dried to constant weight under vacuum.

Syntheses of Copolymers

Poly(1-(2-carbomethoxyacryloyl)-5-fluorouracil-*co*-styrene) [Poly(CMAFU-*co*-St)]

Copolymerization of CMAFU with St was carried out with AIBN in cyclohexanone at 60°C. For determination of the monomer reactivity ratios, a series of polymerizations in which the feed ratio of CMAFU (M_1) to St (M_2) was varied

in cyclohexanone (from 0.50 to 2.50) yielded copolymers over a wide range of compositions. Copolymerization was adjusted to make conversion below 10% by controlling the reaction time. Taking a copolymer with $M_1/M_2 = 1$ as an example, a solution of 1.21 g (5 mmol) CMAFU, 0.52 g (5 mmol) St, and 0.103 g AIBN in 25 mL dry cyclohexanone was introduced into a dry polymerization tube. The tube was sealed after being degassed twice by purging with purified N_2 gas and placed in a regulated thermostat at 60 ± 0.05°C for specified time periods. The polymer solution obtained was precipitated in excess *n*-hexane. The precipitate was collected by filtration and dried to constant weight under vacuum.

Poly(1-(2-carbomethoxyacryloyl)-5-fluorouracil-*co*-methyl methacrylate) [Poly)CMAFU-*co*-MMA)]

Poly(CMAFU-*co*-MMA) was prepared by the copolymerization of CMAFU with MMA. The procedure was the same as that of poly(CMAFU-*co*-St).

Poly(1-(2-methacryloyloxyethyl)-5-fluorouracil-*co*-methyl methacrylate) [Poly(MAOEFU-*co*-MMA)]

The synthesis of poly(MAOEFU-*co*-MMA) was the same as that described for poly(CMAFU-*co*-MMA) except for the monomer pair.

Analyses of Copolymer Compositions

The copolymer compositions in poly(CMAFU-*co*-St) and poly(CMAFU-*co*-MMA) were determined by quantitative infrared (IR) spectroscopy (Perkin-Elmer 1330) according to the literature [14, 15]. For the analysis of poly(CMAFU-*co*-St), a given amount of copolymer was dissolved in *N,N*-dimethylformamide (DMF) of spectrophotometric grade. The solution was placed in a liquid cell, and quantitative analysis was performed on the IR spectrum. The composition of CMAFU was determined by a characteristic peak of N—H out-of-plane bending at 815 cm^{-1}. For poly(CMAFU-*co*-MMA), a liquid cell filled with the copolymer solution of 2-methoxyethanol (spectrophotometric grade) was used for analysis. A quantitative analysis of copolymer composition was done by using a characteristic peak at 790 cm^{-1}. The composition of the copolymer samples was also determined by elemental analysis (Perkin-Elmer 240C Elemental Analyzer) and correlated with their respective IR spectra to give a calibration curve. For poly(MAOEFU-*co*-MMA), the copolymer compositions were determined by using a UV spectrophotometer (Hitachi 220). The specific absorptivities of the polymers were measured at 268.5 nm in 1,2-dimethoxyethane.

Measurement of Intrinsic Viscosity

The intrinsic viscosity (η) of the polymers was measured in tetrahydrofuran (THF) at 30 ± 0.01°C with a Cannon-Fenske viscometer.

Toxicity Test

The toxicity of 5-FU, CMAFU, MAOEFU, poly(MAOEFU), poly(CMAFU-*co*-St), poly(CMAFU-*co*-MMA), and poly(MAOEFU-*co*-MMA) against *D. melanogaster* was tested by the Lewis and Bacher adult feeding method. The composi-

tions of CMAFU and MAOEFU in poly(CMAFU-*co*-St), poly(CMAFU-*co*-MMA), and poly(MAOEFU-*co*-MMA) used as test samples were 50, 48, and 43 wt%, respectively. The intrinsic viscosities of poly(CMAFU-*co*-St), poly(CMAFU-*co*-MMA), poly(MAOEFU), and poly(MAOEFU-*co*-MMA) used were 0.07, 0.09, 0.09, and 0.08, respectively.

D. melanogaster was cultured in a standard medium [12]. Except when needed for counting or transferring, the cultures were kept in a constant-temperature cabinet at 25°C over all experimental runs. The treatment medium for the control group consisted of 5% sucrose in an ethanol–water (1:1, v/v) mixture. For other experimental groups, 1000 ppm of CMAFU, MAOEFU, poly(MAOEFU), poly(CMAFU-*co*-St), poly(CMAFU-*co*-MMA), or poly(MAOEFU-*co*-MMA), respectively, was added to the treatment solution. Every 12 h the number of dead flies was scored for each experimental group.

RESULTS AND DISCUSSION

Monomer Reactivity

Poly(CMAFU-*co*-St) or Poly(CMAFU-*co*-MMA)

The compositions of poly(CMAFU-*co*-St) and poly(CMAFU-*co*-MMA) were determined by quantitative IR analyses. The absorptions at 815 and 790 cm^{-1}, assigned to the out-of-plane N—H bending vibration in the CMAFU unit, were selected as the characteristic frequencies for analyses of poly(CMAFU-*co*-St) and poly(CMAFU-*co*-MMA), respectively, because PMMA and polySt showed no absorbance at these frequencies. The copolymer compositions in poly(CMAFU-*co*-St) are listed in Table 1.

The reactivity ratio of each monomer was estimated by the Kelen-Tüdös method [16]. Figure 1 shows a typical Kelen-Tüdös plot to determine monomer reactivity ratios, in which the ordinate η and the abscissa ξ are explained in Table 1 along with several other parameters.

The Kelen-Tüdös plot gives an r_1 value of 0.01 (CMAFU) and an r_2 value of 7.46 (St). Since r_1 (k_{11}/k_{12}) is much less than unity and r_2 (k_{22}/k_{11}) is larger than unity for the copolymerization of CMAFU with St, the reaction between CMAFU radical and St monomer occurs more readily than that between CMAFU radical and CMAFU monomer. This may be attributed to the steric hindrance of CMAFU.

In order to know the steric hindrance effect of a monomer containing 5-FU in more detail, we also determined the monomer reactivity ratio for the copolymerization of CMAFU with MMA by the same method as described for the copolymerization of CMAFU with St. By the Kelen-Tüdös method, the r_1 and r_2 values of copolymerization of CMAFU with MMA were given as followings: r_1 (CMAFU) = 0.01, r_2 (MMA) = 35.08. As in the copolymerization of CMAFU with St, each reactivity ratio clearly shows the steric hindrance effect of CMAFU. The copolymer compositions are summarized in Table 2. Several other parameters related to the Kelen-Tüdös plot are also shown in the same table.

TABLE 1. Kelen-Tüdös Parameters for Determination of Monomer Reactivity Ratios for the Copolymerization of CMAFU (M_1) and St (M_2). $\alpha = 10.21$

No.	$X = \frac{M_1}{M_2}$	$Y = \frac{m_1}{m_2}$	X^2	$Y - 1$	$F = \frac{X^2}{Y}$	$G = \frac{X(Y-1)}{Y}$	$\alpha + F$	$\eta = \frac{G}{\alpha + F}$	$\xi = \frac{F}{\alpha + F}$
1	0.50	0.06	0.25	−0.94	4.17	−7.83	14.38	−0.54	0.29
2	1.00	0.13	1.00	−0.87	7.69	−6.69	17.89	−0.37	0.43
3	1.50	0.18	2.25	−0.82	12.50	−6.83	22.71	−0.30	0.55
4	2.00	0.22	4.00	−0.78	18.18	−7.09	28.39	−0.25	0.64
5	2.50	0.25	6.25	−0.75	25.00	−7.50	35.21	−0.21	0.71

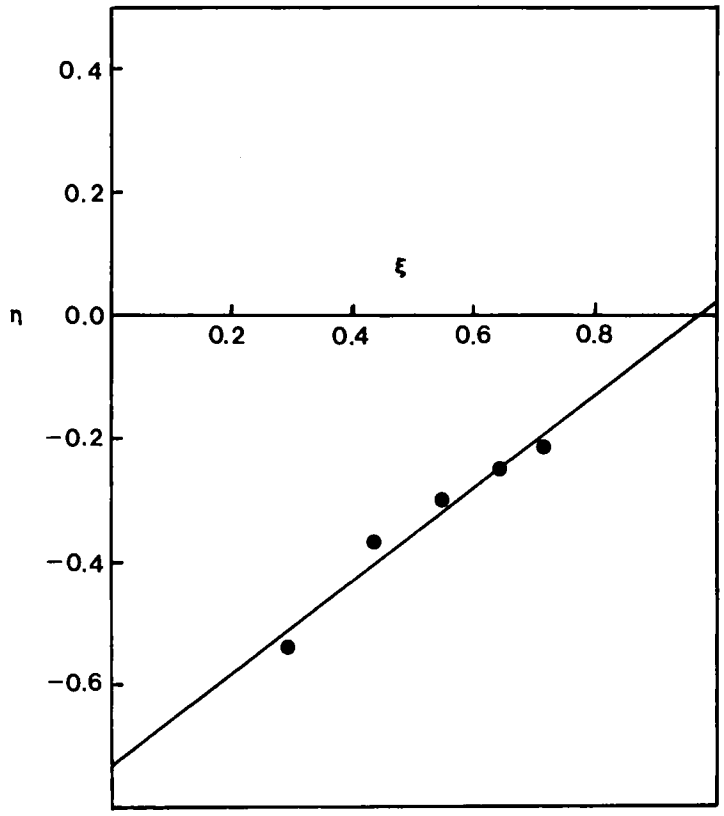

FIG. 1. Kelen-Tüdös plot for the copolymerization of CMAFU and styrene r_1 (CMAFU) = 0.01, r_2 (St) = 7.46.

Poly(MAOEFU-*co*-MMA)

The composition of the monomer unit in poly(MAOEFU-*co*-MMA) was analyzed by using UV spectroscopy. The UV spectra of poly(MAOEFU) and PMMA in 1,2-dimethoxyethane were measured at 268.5 nm, and the following equation was derived from the relationship between the specific absorptivity of copolymer (k) and the weight fraction (x) of the MAOEFU unit in the copolymer:

$$x = 0.334k - 0.003$$

The copolymer compositions are listed in Table 3 along with other values necessary for further calculations in the Kelen-Tüdös plot.

From the Kelen-Tüdös plot, r_1 and r_2 values were estimated as 0.77 (MAOEFU) and 1.13 (MMA), respectively. These data also show that the reaction of MAOEFU radical and MMA monomer occurs more readily than that of MAOEFU radical and MAOEFU monomer. The results may be ascribed to the steric hindrance of MAOEFU.

TABLE 2. Kelen-Tüdös Parameters for Determination of Monomer Reactivity Ratios for the Copolymerization of CMAFU (M_1) and MMA (M_2). $\alpha = 39.93$; r_1 (CMAFU) = 0.01 and r_2 (MMA) = 35.08

No.	$X = \frac{M_1}{M_2}$	$Y = \frac{m_1}{m_2}$	X^2	$Y - 1$	$F = \frac{X^2}{Y}$	$G = \frac{X(Y-1)}{Y}$	$\alpha + F$	$\eta = \frac{G}{\alpha + F}$	$\xi = \frac{F}{\alpha + F}$
1	0.50	0.014	0.25	−0.99	17.85	−35.21	57.79	−0.61	0.31
2	1.00	0.026	1.00	−0.98	38.46	−37.46	78.39	−0.48	0.49
3	1.50	0.043	2.25	−0.96	52.33	−33.38	92.26	−0.36	0.57
4	2.00	0.056	4.00	−0.94	71.43	−33.71	111.36	−0.30	0.64
5	2.50	0.070	6.25	−0.93	89.29	−33.21	129.22	−0.26	0.69

TABLE 3. Kelen-Tüdös Parameters for Determination of Monomer Reactivity Ratios for the Copolymerization of MAOEFU (M_1) and MMA (M_2). $\alpha = 0.90$; r_1 (MAOEFU) = 0.77 and r_2 (MMA) = 1.13

No.	$X = \frac{M_1}{M_2}$	$Y = \frac{m_1}{m_2}$	X^2	$Y - 1$	$F = \frac{X^2}{Y}$	$G = \frac{X(Y-1)}{Y}$	$\alpha + F$	$\eta = \frac{G}{\alpha + F}$	$\xi = \frac{F}{\alpha + F}$
1	0.25	0.21	0.06	−0.79	0.30	−0.94	1.19	−0.79	0.24
2	0.47	0.41	0.22	−0.59	0.54	−0.68	1.43	−0.48	0.38
3	1.00	0.86	1.00	−0.14	1.16	−0.16	2.05	−0.08	0.57
4	1.50	1.26	2.25	0.26	1.79	0.31	2.68	0.12	0.67
5	2.13	1.65	4.54	0.65	2.75	0.84	3.64	0.23	0.76

Toxicity of Materials

The effects of 5-FU, CMAFU, poly(CMAFU-*co*-St), and poly(CMAFU-*co*-MMA) on the mortality of *D. melanogaster* are shown in Fig. 2. For a control group there is no significant change in mortality up to 516 h. However, the mortality of *D. melanogaster* treated with other experimental groups increased remarkably after about 250 h. The lethal times at which all treated males died are 360, 432, 380, and 408 h for 1000 ppm of 5-FU, CMAFU, poly(CMAFU-*co*-St), and poly-(CMAFU-*co*-MMA), respectively. We found from this experiment that the toxicity follows the order 5-FU > poly(CMAFU-*co*-St) > poly(CMAFU-*co*-MMA) > CMAFU > control.

Figure 3 shows the effects of 1000 ppm of 5-FU, MAOEFU, poly(MAOEFU), and poly(MAOEFU-*co*-MMA) on the mortality of *D. melanogaster*. The trend is similar to that of CMAFU and its copolymers. *D. melanogaster* fed with only 5% sucrose solution (control group) shows no significant change in mortality up to 456 h. However, the mortality of *D. melanogaster* treated with other experimental groups increased considerably after about 250 h. The lethal times at which all male flies died are 360, 424, 445, and 400 h for 5-U, MAOEFU, poly(MAOEFU), and poly(MAOEFU-*co*-MMA), respectively. The toxicity decreased in the order 5-FU > poly(MAOEFU-*co*-MMA) > MAOEFU > poly(MAOEFU) > control.

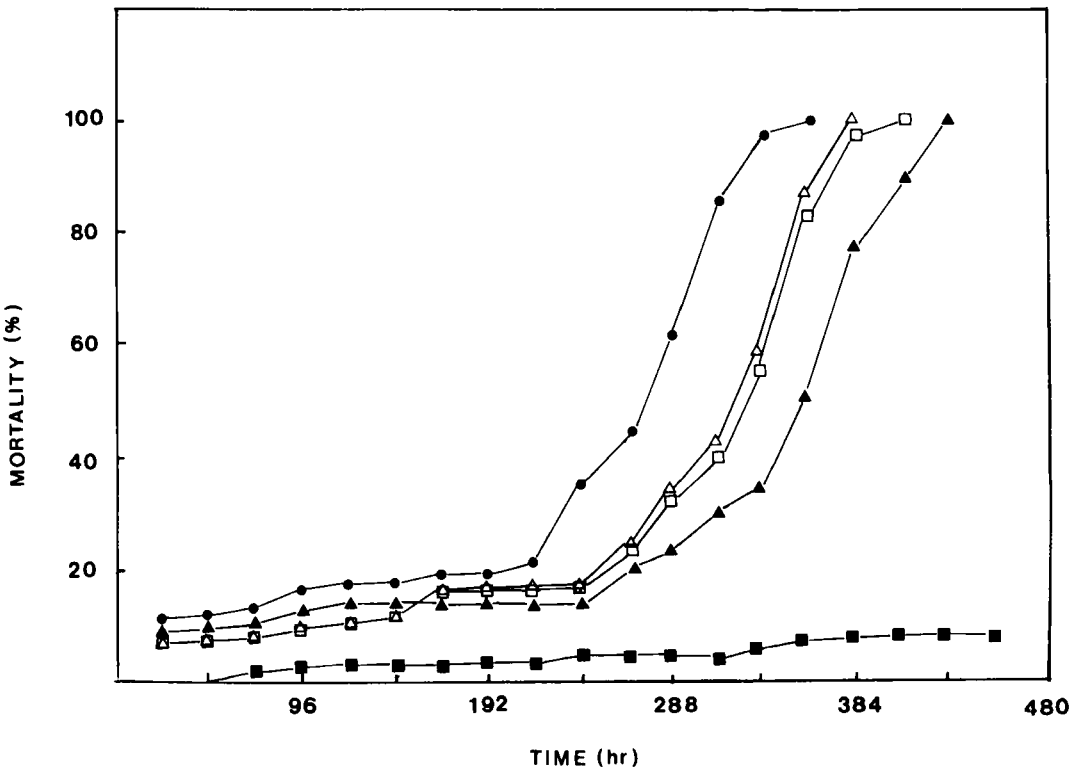

FIG. 2. Exposure-mortality relationship for OR males treated with various chemicals after adult feeding (1000 ppm): (■) control group, (●) 5-FU, (▲) CMAFU, (△) poly(CMAFU-*co*-St), (□) poly(CMAFU-*co*-MMA).

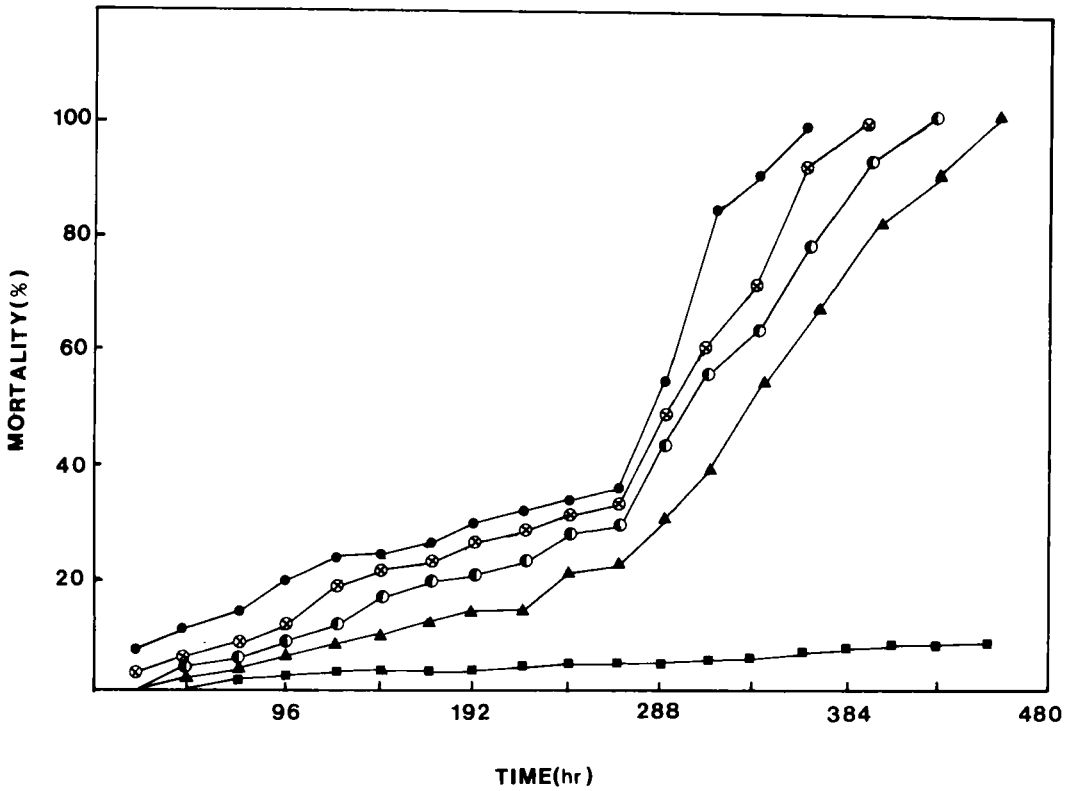

FIG. 3. Exposure-mortality relationship for OR males treated with various chemicals after adult feeding (1000 ppm): (■) control group, (●) 5-FU, (◐) MAOEFU, (▲) poly-(MAOEFU), (⊗) poly(MAOEFU-*co*-MMA).

CONCLUSIONS

The monomers 1-(2-carbomethoxyacryloyl)-5-fluorouracil (CMAFU) and 1-(methacryloyloxyethyl)-5-fluorouracil (MAOEFU) were synthesized from 2,4-bis(trimethylsilyloxy)-5-fluoropyrimidine (BTMSF). Poly(MAOEFU) was obtained by radical polymerization with AIBN in cyclohexanone at 60°C. Copolymerizations of 1-(2-carbomethoxyacryloyl)-5-fluorouracil (CMAFU) or 1-(2-methacryloyloxy-ethyl)-5-fluorouracil (MAOEFU) with methyl methacrylate (MMA) or styrene were carried out with AIBN at 60°C. The copolymer compositions were analyzed by IR or UV spectroscopy. The monomer reactivity ratios r_1 and r_2 were determined by the Kelen-Tüdös method: r_1 (CMAFU) = 0.01 and r_2 (St) = 7.46; r_1 (CMAFU) = 0.01 and r_2 (MMA) = 35.08; r_1 (MAOEFU) = 0.77 and r_2 (MMA) = 1.13. These values imply that the copolymerizations were significantly affected by the steric hindrance of monomers containing 5-fluorouracil (5-FU). The toxicities of monomers and polymers synthesized against *Drosophila melanogaster* were investigated by the adult feeding method of Lewis and Bacher. The toxicity decreased in the order 5-FU > copolymers > monomers > homopolymer.

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