THE SYNTHESIS, POLYMERIZATION, AND COPOLYMERIZATION OF 1-(N-2-ETHYLMETHACRYLCARBAMOYL)-5-FLUOROURACIL

by

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ABSTRACT

THE SYNTHESIS, POLYMERIZATION, AND COPOLYMERIZATION OF 1-(N-2-ETHYLMETHACRYLCARBAMOYL)-5-FLUOROURACIL

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A polymerizable derivative of 5-fluorouracil (5-FU) was prepared using isocyanatoethylmethacrylate (IEM). This monomer was then polymerized and also copolymerized with methyl acrylate (MA), butyl acrylate (BA), methyl methacrylate (MMA), butyl methacrylate (BMA), stearoyl methacrylate (StMA), and hydroxyethyl methacrylate (HEMA). The products of these reactions may find use as slow release systems for the delivery of 5-FU in anticancer chemotherapy, reducing the side effects of this drug. The proposed products prepared were: 1) 1-(N-2-ethylmethacrylcarbamoyl)-5-fluorouracil (EMCF); 2) poly[EMCF]; 3) 25% MA/75% EMCF copolymer; 4) 50% MA/50% EMCF copolymer; 5) 75% MA/25% EMCF copolymer; 6) 25% BA/75% EMCF copolymer; 7) 50% BA/50% EMCF copolymer; 8) 75% BA/25% EMCF copolymer; 9) 25% MMA/75% EMCF copolymer; 10) 50% MMA/50% EMCF copolymer; 11) 75% MMA/25% EMCF copolymer; 12) 25% BMA/75% EMCF copolymer; 13) 50% BMA/50% EMCF copolymer; 14) 75% BMA/25% EMCF copolymer; 15) 25% StMA/75% EMCF copolymer; 16) 50% StMA/50% EMCF copolymer; 17) 75% StMA/25% EMCF copolymer; 18) 25% HEMA/75% EMCF copolymer; 19) 50% HEMA/50% EMCF copolymer; 20) 75% HEMA/25% EMCF copolymer; 21) poly[MA); 22) poly[BA]; 23) poly[MMA]; 24) poly[BMA]; 25) poly[StMA]; 26) poly[HEMA]; 27) 1-(N-2-ethylmethacrylcarbamoyl)-

uracil; 28) poly[1-(N-2-ethylmethacrylcarbamoyl)uracil]; 29) 1-(N-2-ethylmethacrylcarbamoyl)piperidine; and 30) poly[1-(N-2-ethylmethacryl-carbamoyl)piperidine]. The last ten were prepared as model compounds. All of the compounds containing 5-FU except the monomer and 75% StMA copolymer were found to be insoluble. The monomer is soluble in 1,4-dioxane, butyl acetate, diethyl ether, methyl ethyl ketone, methyl isobutyl ketone, and tetrahydrofuran. The assigned structures of EMCF, its polymer, and copolymers are supported by infrared spectroscopy. Their spectra show an amide III band in the 1330-1345 cm^{-1} region, and the monomer also shows two double bond bands at 940 cm^{-1} and 970 cm^{-1} which are absent in the polymers.

Piperidine, uracil, and 5-FU reacted readily with IEM in 1,4-dioxane in the presence of triethylamine as the catalyst. Polymerization of all monomers in this study occurred in 1,4-dioxane using azobisisobutyronitrile as the initiator. Elemental analysis showed a discrepancy in the amount of EMCF in the homopolymer and copolymers than theoretically calculated. This may be due to thermal decomposition of the monomer at the reaction temperature of 80°C. Further study is needed to confirm this.

Hydrolysis studies were run on 5-FU, EMCF, poly[EMCF], the three MA copolymers, and the three BA copolymers to determine the relative release rate of 5-FU from each. These tests confirm two hypotheses: 1) as the percentage of EMCF decreases in the polymer, the release rate of 5-FU decreases, and 2) as the hydrophobicity of the polymer increases, the release rate of 5-FU decreases. The most intriguing property of these systems is their zero order release kinetics, making

it possible for them to deliver 5-FU at a constant rate for an extended period of time.

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CHAPTER I

GENERAL INTRODUCTION AND HISTORICAL

The Development of Cancer Chemotherapy

Bacteria were discovered by A. Leeuwenheck in 1675. Semmelweis recognized this relationship between bacterial infection and mortality in 1850, but his theories were unfortunately dismissed at that time. Lister then provided the principle of antisepsis and this, along with the germ theory put forth by Pasteur and Koch, gave birth to medical microbiology.[1]

In 1906, another breakthrough in medicine was conceived by Paul Ehrlich while working on dyes-the idea that treating infections was possible by synthesized chemicals rather than protein antibodies. After 606 tries, he finally developed the first chemotherapeutic agent. This fathered the modern drug industry.[1,2]

Cancer chemotherapy had its birth in "work on potential war gasses, which led to the discovery of the clinical value of nitrogen mustard, di-(2-chloroethyl)methylamine, in Hodgkin's disease and certain related conditions."[3] The first anti-cancer agents were the alkylating agents which are active compounds that alkylate such biologically important compounds as DNA, RNA, and certain enzymes. During WWI, the observation was made that individuals gassed with mustard gas, bis(β-chloroethyl)sulfide, suffered damage to their body's bone marrow and lymphoid tissues. Subsequent animal studies during WWI showed that heavy exposure to various nitrogen mustards destroyed lymphoid

tissues; hence the idea to use these compounds to treat patients with cancers of the lymphoid tissues. They were successfully used for a short time, but the patient's healthy, normal bone marrow was damaged to the extent that further treatment with the mustards was precluded.[4]

Since these alkylating agents rely on the electron releasing capacity of their nitrogen atom, and since aromatic amines are generally less basic than aliphatics, compounds replacing the methyl group in nitrogen mustard (called Mustragen or Mechlorethamine) with various electron-withdrawing groups were made. These compounds were given by mouth, being less reactive and thus more mild.[4] One such derivative was Uracil Mustard (Figure 1). It suppresses the synthesis of acidic nuclear proteins inhibiting the incorporation of precursors into nucleic acids and also incorporation of amino acids into t-RNA. Less than 1% is recovered in the urine and none is present in the blood 2 hours after administration. It is used in treating Hodgkin's disease, chronic lymphatic leukemia, lymphosarcoma, and carcinoma of the breastand ovary. Its trade name is DOPAN. Side effects from it include bone marrow depression, some nausea, vomiting, diarrhea, and dermititis.[5,6,7] Uracil mustard is an example of a "carrier" moiety, uracil, attached to a "warhead" moiety, the mustard group.[3]

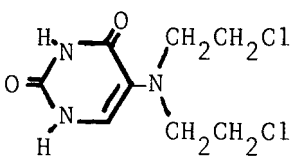


Figure 1-Uracil Mustard

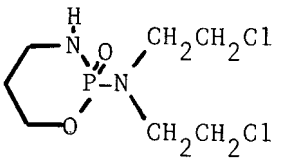


Figure 2-Cyclophosphamide

Another derivative of the nitrogen mustards still used in treatment of Hodgkin's disease, as we11 as breast, ovarian, and lung cancers is cyclophosphamide (Figure 2).[4]

The alkylating agents such as nitrogen mustards "may produce mutations in at least 3 ways: 1) addition of methyl or ethyl groups to guanine, causing it to behave as a base analog of adenine and thereby producing pairing errors; 2) loss of alkylated guanine bases (depurination), producing gaps in the DNA replication or cause a shortened nucleotide sequence; and 3) crosslinking between the strands of the same or different DNA molecules causing loss or excision of nucleotides.",[8]

Further research by Woods led to the discovery in 1940 that the antibacterial action of sulfanilamide was overcome by p-aminobenzoic acid and there were great expectations that the magical formula of chemotherapy had been uncovered. Many scientists and physicians felt it was necessary only to select a metabolite and make an antimetabolite to inhibit its pathway. For example, in 1945-1947 Limarzi et al tried 2-thiouracil in the treatment of leukemia after observing leucopenia and agranulocytosis in patients treated for hyperthyroidism with this drug. It had no value in treating leukemia.[7] Many other attempts using this type of approach also failed,[9] but researchers continued to try to unlock the door to cancer chemotherapy using this method.

One such group was Farber et al, who in 1947 obtained the first remission of cancer using chemotherapy. Efforts to find antagonists inhibiting the synthesis of nucleic acids increased. These antagonists inhibit by mainly competitive mechanisms. One

group is the antimetabolites.[10] The discovery in 1954 by Putnam, Cantarow, and Paschkis of the enhanced utilization of uracil for DNA biosynthesis in rat hepatoma, as opposed to the normal cell's use of orotic acid,[11] led Heidelberger et al and Duschinsky et al, through collaboration, to prepare just such an antimetabolite of uracil in 1957.[5,6,12,13,14,15,16]

Heidelberger knew the substitution of a fluorine for a hydrogen in certain biologically active molecules drastically modifies their biological activity. The smallness of the fluorine atom enables it to fit in place of hydrogen, but the stability of the carbon-fluorine bond prevents biological reactions from taking place.[7,14,15,17] Therefore, he synthesized 5-fluorouracil (5-FU), which has been used since then to treat certain cancers.[15,18] Other uracil related purine and pyrimidine derivatives synthesized with this end in mind are given on Table 1.

Research on 5-Fluorouracil

Heidelberger went on to show that the LD_{50} for 5-FU in rats is approximately 200 mg/kg and the maximum tolerated dose over 10 days is 25 mg/kg. The formation α-fluoroacetic acid from fluorouracil was suggested as the cause of side effects from large doses-convulsions and cardiac acitivity change in animals.[7] Duschinsky et al synthesized 5-fluorodeoxyuridine and 5-fluorouridine, attempting to reduce or eradicate these side effects. The former was found to do so [13,15] and the latter has been found to inhibit Rous Sarcoma Virus though it does not decrease side effects.[34] Heidelberger had shown the effectiveness of 5-FU in treating sarcoma 180 and other tumors in rats and mice. Curreri et al at the University of Wisconsin Hospitals

TABLE 1

URACIL AND RELATED PURINE AND PYRIMADINE DERIVATIVES

Uracil Derivatives

1-acryloyluracil[19]

N-(N'-allylcarbamoyl)uracil[19]

5-(2-amino-4-thiazolyl)uracilhydrobromide[20]

5-aminouradine[21]

6-azauracil — made by Sorm, Hanschumaker, and Welch in 1956. Bieber et al in 1957 found that is has little effectiveness against tumors[7]. It produces CNS symptoms.[22]

6-azauridine — Skoda et al studied in 1957, Pasternak and Hanschumaker in 1958. Found some effectiveness against tumors.[7] Particularly effective against cells if they are dependent on the de novo pathway.[5] It is transiently effective in some leukemias.[13] It blocks the decarboxylation of orotic acid to form uracil.[14] It inhibits conversion of orotate into UMP and also into pseudouridine in RNA.[13]

5-bromoacetyluracil[20]

5-butyl-2'-deoxyuridine — showed antiviral activity against DNA and RNA viruses.[23,24,25]

1-(N-ethylcarbamoyl)uracil[19]

5-ethyl-2'-deoxyuridine — has potent antiviral acitivity.[26]

ethyl trans-3-(5-uracily1)propenate

5-fluoro-5-bromo-6-methoxy-5,6-dihydro-2'-deoxyuridine-5'-monophosphate— sythesized by Duschinsky in 1964. Had inhibitory effect on thymine synthetase.[15]

5-formamidouridine.[21]

5-formyluracil[20]

5-glycolyluracil[20]

5-glycolyluracil hydrobromide hemihydrate[20]

5-hydroxymethyluracil acrylate[27]

5-hydroxymethyluracil methacrylate[27]

TABLE 1 (CON'T)

URACIL AND RELATED PURINE AND PYRIMADINE DERIVATIVES

Uracil Derivatives

5-hydroxyuridine[21]

5-(imidazol-2-yl)uracil[20]

5-(imidazol-4-yl)uracil[20]

N-(2-methacryloyloxy)ethyl uracil[28]

3-methyl-5-aminouridine[21]

3-methyl-5-bromouridine[21]

3-methyl-5-chlorouridine[21]

4-methyl-5-[2-fluoroethyl(2-chloroethyl)amino]uracil — (Fluoropan) found to be less toxic to normal tissues and have increased antitumor activity by Nemitz et al in 1957.[7]

5-methyluridine[21]

5-nitrouracil[21]

5-N,N-dimethyl-B-alanyluracil hdrochloride[20]

6-methyl-2-thiouracil[29]

5-(2-propynyloxy)-2'-deoxyuridine — potent inhibitor against Herpes Simplex virus.[30]

2-thiouracil [29]

trans-3-(5-uracilyl)propenoic acid[20]

5-(trifluoromethyl)-2'-deoxyuridine[13]

5-trimethylammoniumacetyluracil bromide[20]

1-(5-uracilyl)buten-3-one[20]

1-(5-uracilyl)-3-dimethylaminopropanol hydrochloride[20]

6-uracilmethyl sulphone — acts as an alkylating agent. Inhibits incorporation of precursors into DNA, apparently by blocking conversion of ribonucleotides into deoxyribonucleotides.[5]

N'-(N-vinylcarbomoyl)uracil[19]

TABLE 1 (CON'T)

URACIL AND RELATED PURINE AND PYRIMADINE DERIVATIVES

Related Purine and Pyrimadine Derivatives

9-acryl-6-methylthiopurine[31]

6-azathymine — made by Prusoff et al in 1954, found to have no clinical value.[7]

5-fluorocytosine[7]

5-fluorocytodine[7]

5-fluorocytodylate — shown to be active against B82 leukemia with a high theraputic index.[7]

6-methlythio-N-allylpurine-9-carboxamide[31]

6-methlythio-N-(vinylcarbamoyl)purine[32]

trifluorothymidine — most powerful drug against DNA viruses known.[14]

9-substituted-6-alkylthiopurines and purine-6-(1H)-thiones[33]

started clinical trials with advanced cancer patients. They found that 5-FU did have signifigant palliative therapeutic value, especially in patients with breast and gastrointestinal cancers.[15]

In 1958, further research on 5-FU progressed. Chaudhuri et al, while investigating with labeled 5-FU in animals and man, found that 10% is excreted in the urine unchanged and then about 10% more is excreted as the conversion products. Radioactive carbon also appears in expired CO_2. Rich et al showed inhibition of human tumor cell cultures occurs at a concentration of 1 γ/ml for 5-FU and 0.01 γ/ml for fluorouridine and fluorodeoxyuridine. Thymine reverses this inhibition.[7] Bosch, Harbers, and Heidelberger found that when Ehrlich ascites cells were incubated with ^{14}C-formate, no formate incorporation into DNA occurred when the fluorinated derivatives fluorooratate, 5-FU, 5-fluorouridine, or 5-fluorodeoxyuridine were present. They found 5-fluorodeoxyuridine to be the most active, and fluorooratate to be the least active.[14] Dannenbert et al showed 5-FU, and to a greater extend 5-FUR and 5-FUDR, to inhibit the incorporation of uridine monophosphate into RNA and conversion or uracil to thymine of DNA. Incorporation of labelled thymine into DNA does not change. From this they postulated that 5-FU inhibits the conversion of formate into the methyl group of thymine in DNA. This suggested the compounds blocked the reactions involved in formation of the methyl group in thymine, causing the cell to die.' This is indeed found to be the mechanism in vitro and in vivo.[4,5,13,14,15,17,18,35,36]

When any chemical substance enters the body, it is distributed throughout according to its solubility in each part. Thus, the "thymineless death" from treatment with 5-FU unfortunately occurs

in normal cells as well, though to a lesser extent than in the cancer cells since 5-FU is taken up more rapidly by cancer cells. Other undesirable side effects are caused by 5-FU such as: nausea, anorexia, redness of the lip and bile mucosa, ulceration of the intestinal mucosa, vomiting, stomatitis, diarrhea, pharingitis, esophatitis, epistaxis, thrombocytopenia, leukopenia, neurological damage, depressed haemporesis, loss of hair, and dermatitis.[6,7,22] The low therapeutic index of 5-FU, or narrow margin between effective anti-cancer dose and mortality, is blamed for these side effects and the major sites of cell necrosis are the bone marrow and gastronintestinal tract. These side effects are due to the conversion of 5-FU in the body to 5-FUR. In man, 5-FUR is 30X as toxic by weight as 5-FU. The attempt to circumvent the problem by synthesizing 5-FUDR helped little because of poor uptake by the cells and its rapid catabolism back to 5-FU.[5,13] Nevertheless, some researchers found 5-FUDR to be less toxic and more effective than 5-FU.[7,14]

Mice with sarcoma 180 which were given labelled 5-FU showed the highest accumulation in tumor, somewhat less in bone marrow, and then in decreasing order in the intestines, spleen, kidneys, and liver. Specific selective accumlation was not observed.[7] In the liver, 5-FU is catabolized to inactive products: dihydrofluorouracil, α-fluorou-β-ureidopropionic acid, α-fluoro-β-alanine, and urea or carbon dioxide and ammonia.[13,15,18] Heidelberger found that certain tumor cells have a very poor degradative capacity for uracil. The same path is also followed by 5-FU.[5,14,18] Sir Rudolph-Peters put forth the principle of lethal synthesis in 1970 which states that a cell may synthesize a lethal

compound from a non-lethal one by normal metabolic pathways. Such is the case for 5-FU.[14]

Treating Humans with 5-Fluorouracil

In cancer treatment in humans, 5-FU has been found useful in treating cancers of the breast, colon, rectum, skin, thyroid, pancreas, kidney, bladder, uterus, cervix, pharnyx, liver, stomach, prostate, and large bowel.[4,5,13,35,36] 5-Fluorouracil also inhibits the growth of these solid tumors: sarcoma 180, adenosarcoma 775 and EO771, Walker carcinosarcoma, ascites tumors (in particular Ehrlich and Yoshida sarcoma) and a number of leukemia strains (for example L1210, B82, other myeloid and lymphoid leukemias and plasma cell, mast cell, and reticular cell tumors).[7]

Since 5-FU is not as effective when given by mouth,[7] in normal treatment it is infused for periods of days to weeks because the turnover rate of DNA is slow.[13,15] The Curreri and Ansfield treatment calls for a high initial "loading" dose, followed by a lower dose until toxic side effects are seen. In the Jacobs Regimen, no loading dose is given.[35] It has been noted that single injections of 5-FU of 15 mg/kg will produce toxicity after 4 to 5 days, whereas the same amount given by continuous infusion was tolerated up to 36 days without toxic side effects. When given by continuous infusion, FUDR increases in toxicity, but the single daily dose is 30 to 60 times as great to give the same biological effects. Also, when FUDR was given by continuous infusion, its therapeutic effects seemed to increase.[37] Meyers, Young, and Chabner have proposed a system where 5-FU would be given based on the differential uptake of 5-FU by cancer cells as opposed to normal cells in the body.[38] Curreri et al also reported on studies where 5-FU and FUDR were used in

adjunctive therapy and increased survival times were noted.[13] 5-FU is also used in conjunction with x-ray therapy.[7,13] Hall and Good first reported using the combination of 5-FU with radiation in 1962. Frank et al also reported in 1962 on a prolonged I.V. drip over 8 hour periods for 10 out of 15 days in conjunction with radiation, but the effects could have been caused by radiation alone.[39] Marked regression of tumors by 5-FU is rarely achieved without manisfestations of relatively severe toxicity to normal tissues.[7,13]

The Biochemistry of Cancer Cells and Immunity to Drugs

Some cancers are immune or develop immunity to the effects of 5-FU. To understand why, one must consider the biochemistry of the cancer cells and the action of the drug. The de novo synthesis of dTMP is limited, at least in leukocytes, by the "thymidylate synthetase" reaction. This pathway was first elucidated in 1956 by Friedkin and his associates.[15] This reaction is not detected in normal hepatic cells, but is high in primary or transplanted hepatomas. Precancerous or regenerating liver has a high activity of this enzyme also. Such a rise was also found in infectious mononucleosis. An increase in the reductase for tetrahydrofolic acid production has been noted in myeloid leukemias. Tetrahydrofolic acid formylase activity was found to be high in both chronic lymphatic leukemia and myeloid leukemia. Such a rise in activity of these enzymes is considered to be a reflection of the increased de novo DNA synthetic ability by non-specific cells.5 Fraudulent monomers act on cancer in one of two ways: 1) to compete successfully with normal monomers in blocking, for example, essential enzymes synthesizing cellular polymers from monomers, or 2) to be incor-

poratedfraudulently into cellular polymers. FUDR is an example of type 1, and 5-bromodeoxyuridine is an example of type 2.[13] The efficacy of purine derivatives, such as 5-FU, in myeloid leukemia, but not most lymphatic leukemias is explained by the sources of nucleotide synthesis in these cells. In myeloid, as well as the other cancers noted above, the source is mostly nucleotides synthesized in the cells by the *de novo* pathway, whereas lymphoma leukemia cells obtain their nucleotides from "salvage" pathways. If these "salvage" pathways are utilized, where thymidine from the breakdown of other tissues or outside sources is used for DNA synthesis, no inhibition occurs.[5,14]

In 1970, Kessel and Woodinsky found that in a series of mouse leukemias the response to FUDR varied inversely to the activity of thymidine kinase, even though this is the enzyme responsible for phosphorylating FUDR to 5-fluorodeoxyuridine monophosphate. This apparent paradox can be explained in that the k_m/k_i of 5-fluorodeoxyuridine for thymidine kinase is about 1000, much greater than the k_m/k_i for deoxythymidine monophosphate, so whatever 5-fluorodeoxyuridine is in the cell is phosphorylated and is very active in inhibiting the enzyme. However, the more thymidine kinase present, the more deoxythymidine is phosphorylated, and the less the inhibitory effect of 5-fluorodeoxyuridine monophosphate.[14] This is consistent with the proposal by Cohen *et al* in 1958 that the inhibition is through a competitive mechanism.[15] Resistance to a drug occurs also because cancer has cells in all stages of evolution. Successive generations of ascites cells showed a fall in uridine kinase activity after each generation was exposed to 5-FU. Heidelberger also found some tumor cells resistant to 5-FU had developed a thymadylate synthetase which was no longer inhibited by the agent. The loss of enzymes to transform FUDR into the nucleotide

may account for the loss of activity of 5-FU in some cases. Also, a decrease in the amount of 5-FU incorporated into RNA was seen in cells resistant to 5-FU.[5,40]

Selective cell destruction, then, becomes more difficult as rapidly proliferating cell populations develop resistance to an anti-metabolite, such as 5-FU, by: 1) elevation in concentration of key enzymes with which the agent interacts, 2) utilizing alternate biosynthetic pathways for key components, and 3) developing transport deficiencies which block the passage of the drug into the cell. Other routes rendering the drug inactive include: 1) excretion, 2) metabolism and then excretion, and 3) intrinsic blocks in the body, such as the "blood-brain barrier."[44] The development of resistance to any one chemotherapeutic agent by cancer cells has given rise to combination chemotherapy. A cell resistant to one has very little chance of being resistant to all drugs in a combination.[4] Consideration of the stage of development of cancer cells also brings to light another point.

Generally, proliferating cells seem to be much more sensitive anticancer agents than nonproliferating cells. Researchers have shown 5-FU has little or no effect on nonproliferating β-cells *in vivo*, but proliferating cells are very sensitive to it.[38,42,43] The survival of cancer cells in tumors treated *in vivo* with chemotherapeutic agents is sometimes satisfactorily explained by considering that DNA replication in proliferating cells "fixes" the damage to DNA molecules by chemotherapeutic agents, whereas the delay in nonproliferating cells allows for more time to repair the damage. Hahn *et al* in 1973 showed that repairs of some potentially lethal damage in solid tumors exposed to bleomycin, cyclophosphamide, or 5-FU *in vivo* most satisfactorily

explained increased survival of stem cells remaining *in situ* after drug administration for *24* hours rather than for *2* hours.[42]

Studies using cytotoxin and 6-mercaptopurine in combination indicate this type of situation may be overcome by achieving the recruitment of cells into the cell cycle and then reaching them in a drug-sensitive state.[42] Perhaps a drug which holds the cells in the S-phase could be used to keep the cells in a susceptible stage. As it is now, 5-FU is used to treat multiple actinic keratosis by topical application and as an intravenously administered treatment of various carcinomas.[44] Mercaptopurine or 6-azathymine have been used in conjunction with 5-FU and these were found to heighten both the therapeutic and toxic effects of 5-FU.[7]

Other Effects of 5-Fluorouracil

Various other effects of 5-FU administration have been noted. A. Lidner and colleagues have shown a rise in the histone:DNA ratio of ascites cells after 5-FU treatment. They have also shown 5-FU to cause abnormal enzyme proteins where a fall in protein bound S-H bonds with a corresponding rise in S-S bonds occurred in ascites cells from mice. The cells also had reduced tryptophan pyrolase induction, showing a reduction in protein synthesis.[5] In cells treated with 5-FU, DNA content decreases, but RNA and protein content increases.[15,17,44]

Chandhuri, Montag, and Heidelberger in 1958 found 5-FU to be incorporated into the non-terminal end of RNA, but not into DNA. Its incorporation into mRNA and tRNA was confirmed in 1969 by Mandel. Incorporation of orotate or uracil into RNA is also inhibited by 5-FU.[5] A certain amount of 5-FU accumulates in the RNA of sarcoma 18, Ehrlich

tumor, liver, and spleen; but not in the DNA.[7] Interesting results occur due to the incorporation of 5-FU into RNA. These are: 1) mutagenesis in RNA viruses, 2) changes in acceptor activities of tRNA's, 3) miscoding in protein synthesis, 4) inhibition of maturation of rRNA in bacteria and mammalian cells, 5) inhibition of enzyme induction in bacteria and rat liver, 6) depression of RNA synthesis of protein, and 7) modification of the composition of RNA.[14,35,36,44]

Other Halogen Derivatives

The other halogen derivatives of uracil have also been studied and found to be incorporated into DNA. The van der Waals radii for hydrogen and fluorine are close, but the radii of chlorine, bromine, and iodine are closer to that of the methyl group of thymine, so fluorouracil acts like uracil, and the others act like thymine in biosynthetic pathways.[13,18]

Cells grown in the presence of 5-bromodeoxyuridine (5-BUDR) and then exposed to fluorescent light are killed, DNA synthesis is inhibited, and a gamut of DNA damage and cytotoxicity occurs in them causing death. Since exposure to fluorescent light alone does not cause this, 5-BUDR is incorporated into DNA, and debromination of 5-BUDR occurs upon exposure to fluorescent light, then it is inferred that debromination is the initial step in the lethal nature of this combination. Debromination of the 5 position followed by uptake of a hydrogen is the proposed mechanism for the lethality of this combination.[42] The same effects were found when cells were grown in the presence of 5-FU and then exposed to UV light by Lozeron, Gordon, Gabriel, Tautz, and Duschinsky in 1964, but the 5-FU was incorporated into RNA, not DNA.[45]

The *in vitro* synthesis of DNA is not affected by 5-bromouridine (5-BUR) and it can replace thymine. It can cause mutations by transversion to the enol form which takes place when tautomerization of the hydrogen at position 1 to the oxygen at carbon 6 takes place, enabling pairing with guanine instead of adenine. In subsequent replications, the 5-BUR may then revert back to its keto form and pair with adenine. The reverse of this is also true, where it is incorporated in the keto form, pairing with adenine, and then when tautomerization takes place, pairing with guanine in subsequent replications.[8,12,46] The same occurrance, though to an extremely small extent, is predicted and found for 5-FU.[47]

5-Bromouracil (5-BU) has been found to have inhibitory effects on thymine stimulated growth in the absence of folic acid.[12] It is found inferior to 5-FU in anticancer activity.[133]

5-Iododeoxyuridine (5-IUDR) is relatively non-toxic, but it can cause conjunctivitis and rhinitis, and in sufficient quantities it can be toxic or lethal. Localized alopecia sometimes occurs in intraarterial infusions. It does not act as an immunosuppressant as does 5-BUDR.[13,22,49] The activity of DNA polymerase is reduced by 5-IUDR. It inhibits the incorporation of thymidine into DNA. It is incorporated into DNA. Incorporation of 5-iodouridine into RNA is accompanied by a sensitization to destruction by irradiation.[5] Both 5-BUDR and 5-IUDR are mutagenic, teratogenic, and oncogenic. A good review of the literature on these to 1978 is found in a paper written by Goz.[49]

Visser found in Neurospora that 5-chlorouridine inhibits growth in the presence of cytidine or uridine, but did not in the presence of uracil.[21] It also causes transversions in DNA.[47]

Shortcomings of Conventional Cancer Chemotherapy

Two major stumbling blocks in the way of successful cancer chemotherapy are the 1) lack of complete sensitivity to cancer cells, resulting in distressing toxicity and side effects in patients; and 2) the inevitability of emergence of resistant cell populations in tumors.[2,15] In traditional cancer therapy, chemotherapy is generally used when surgery or radiotherapy can no longer control the disease. When surgery and/or radiotherapy are followed by chemotherapy, the success rate has been greatly increased.[4]

One of the biggest problems in treating cancer with chemotherapy comes from the diffusion of the drug into other tissues, producing unwanted side effects. According to Gebelein, "If it were desired to place a 1.0 mg drug dose at a 500 g disease site in a 70 kg person, the total drug dose would have to be a 140.0 mg size sample. This means that about 99.3% of this drug does not reach the target and interacts with other areas instead."[32] Chemically modifying the drug is not likely the answer either, since simple modifications change the drug greatly, and not always in the desired direction.[32] Indeed, it has been shown using uridine derivatives that the nature and position of a modifying group has an effect on a drug's ability to produce the desired inhibition.[21]

Another shortcoming of conventional drug treatment is the "sawtooth" delivery of the agent. The patient receives a large initial dose above the therapeutic dose. This concentration may cause unwanted, even hazardous side effects. The drug level then drops off into the therapeutic range, continuing to drop until it is below the therapeutic range and a new dose is needed, again producing a high level of drug in

the person. This causes a cycle of high, low, then high level of drug in the patient, rather than a consistant level in the therapeutic range. For some drugs, such as 5-FU, their therapeutic and toxic levels are very close together, causing the need for closely controlled levels of drug in the body.[50,51] The short duration of drug action in the therapeutic range has two other detrimental side effects in that the required high frequency of dose administration leads to failure of compliance by the patient, and the inability to use pharmacological agents with short half-lives.[51]

Another consideration in systemic chemotherapy is that the cancer patient is susceptible to infections due to his tumor. According to Rodrigez, "Most antitumor agents also cause myelosuppression, immuno-suppresion, and ulceration of the gastrointestinal tract, which facilitates invasion by enteric organisms. The use of combination chemotherapy has increased our capabilities of treating patients with extensive malignancies, but has also increased their susceptibility to infectious complications . . . Infection is the major cause of death in cancer patients."[52] Even the least toxic drugs can cause damage to other parts of the body, most notably the intestinal epithelium and bone marrow.[5] Another problem in overcoming the immunosuppressive effects of anticancer chemotherapy is that some drugs may decrease the activity of the anti-cancer drug if not given in the proper sequence.[53]

Owing to the immunosuppressive effects of systemic chemotherapy and radiation, the patient also has the increased risk of developing another form of cancer.[54,55]

In 1965, Reid noted three approaches to achieving limited selectivity by anticancer drugs. These were: 1) regional perfusion,

2) using a protective group which would be hydrolyzed off allowing the drug to work in low pH cancer cells (an example of this is 5-fluoro-oratate, which is more reactive in acidic environments), and *3)* to attach drugs to antibodies against tumor-specific antigens.[5] One study using a regional, as opposed to a systemic, treatment of a rhabdomyosarcoma transplanted in one auricle of the heart in the rat, a 50% decrease in the amount of methotrexate needed for therapy was noted.[56]

Various Approaches for Controlled Drug Therapy Using Polymers

By using polymers to regulate drug delivery we can open up a whole new era in drug delivery systems.[1,57] To quote Zaffaroni, "It is my feeling that the real opportunities for new breakthroughs in pharmaceutical research will come mainly through development of controlled delivery systems."[51] Controlled drug release systems are a combination of the drug and excepient, usually a polymer, designed to deliver the drug at a controlled dosage at a controlled rate to a target tissue or organ. The polymer may be biodegradable, releasing the drug by erosion of the polymer; non-biodegradable, releasing the drug through the polymer matrix; or both.[58] More specifically, there are four components in a polymeric drug therapy system: 1) the drug, 2) the drug delivery module for delivering drug, *3)* the platform which contains the drug delivery module coupling the system into the tissue site, and *4)* a drug program built in to deliver the drug at the specified rate and duration to achieve the therapeutic effect.[51] One of the first of these systems is found in a patent issued in *1946* for pellets consisting of a dispersion of desiccated hormone in a waxy media as a new system for a slow and prolonged release of active materials.[59]

Some of the ways polymers are now used in chemotherapy include plastic drug administration devices, biomedical polypeptides, controlled release drug systems, synthetic enzyme-like polymers, bound enzymes, polymeric drugs, and drug carriers.[57,60] Composites of drugs and polymeric matrices are under investigation as fertility control agents, narcotic antagonists, anticancer agents, weight gaining agents for beef cattle, and for treatment of glaucoma and ulcers.[59] Other uses of polymers in medicine are listed in TABLE 2 by the type of polymer involved. The objectives of design in chemotherapeutic polymeric drugs are given in TABLE 3, although, according to Gebelein, "the primary object in these areas is to treat a diseased organ or tissue more directly or selectively without producing an adverse interaction with other parts of the body which would result in undesired toxic side effects."[57] Polymeric implants have advantages over metals or ceramics. Polymers can be easily fabricated into many forms, are non-corrosive in the body, other substances can be incorporated into them by direct bonding, the adhesive polymers can be used as a nonsuturing method of closing wounds or torn organs or hold implants in place and their density is closer to that of natural tissues.[61]

Polymeric drugs are a relatively new approach to the use of polymers in medicine. The drug is attached to or contained in the backbone. This polymer could then be the source of controlled release of a biologically active agent itself. Hundreds of such compounds have been made in the last decade. The drug can be entrapped in the system in another type of approach without being attached at all.[22] There are three basic ways, then, of designing polymeric drugs: 1) to bond the drug to a preformed polymer, 2) to prepare a polymerizable monomer drug, then

TABLE 2

POLYMER USES IN MEDICINE

Acrylics

Aneurysms[62]

Artificial eyeballs[63]

Bile duct[62]

Bone cement[63]

Coating to prevent caries[64]

Contact lenses[65]

Controlling bleeding [66]

Corneal prosthesis[62,65]

Cranial prosthesis[67,68]

Dental resins[63,64,69,70]

Detachment of orbital flooring[71]

Drug delivery systems[2,32,57,72,73]

Ear prosthesis[67]

Filling [74]

Fixation of prosthetic joints[67]

Fixation of fractures[67]

Glaucoma drainage device[65]

Intraocular lens[63,65,67]

Joint replacement[75]

Nerve repair[62]

Non-suture closure[62]

Nose prosthesis[67]

Orbital fractures[67]

Orthopedic prosthesis[76]

TABLE 2 (CON'T)

POLYMER USES IN MEDICINE

Acrylics

Penile inserts[67]

Pleural cavity prosthesis[62]

Rhinoplasty[62]

Soft contact lens[63]

Soft tissue replacement[77]

Spinal fixation[67,68]

Testicular implants[67]

Thoracic deformities[67]

Tooth replica implants[64,67]

Tissue adhesive[62,78]

Vertebral replacement[68]

Cellulosics

Artificial aneurisms[62]

Dialysis membranes[79]

Hemostatic agents[62]

Hernia repair[62]

Nerve repair[62]

Non-suture closure[62]

Soft tissue replacement[77]

Collagen

Heart valves[62]

Cotton

Sutures[80]

TABLE 2 (CON'T)

POLYMER USES IN MEDICINE

Dacron

Aneurysms[81]

Arterial replacement[57,62,81]

Artificial breast wall[62]

Artificial heart wall[62]

Dural substitute[62,69]

Pleural cavity prosthesis[62]

Soft tissue replacement[77]

Sutures[80]

Synthetic ligatures[62]

Dextran

Drug carrier[82]

Plasma substitute[83]

Skin substitute[82]

Epoxy

Aneurisms[62]

Encapsulated implants[62,84]

Soft tissue replacement[77]

Gelatins

Contact lenses[62]

Dural substitute[62]

Hemostatic agents[62]

Perforated eardrum[62]

Plasma substitute[83]

TABLE 2 (CON'T)

POLYMER USES IN MEDICINE

Hydroxyethyl Starch

Plasma substitute[77]

Nylon

Arterial replacement[62]

Facial repair[62]

Fracture of orbital flooring[71]

Hernia repair[62]

Protruding ear[62]

Soft tissue replacement[62,77]

Sutures[77,79]

Synthetic ligatures[62]

Tendon repair[62]

Perfluorodecalin

Blood substitute[63]

Poly (acrylonitrile)

Soft tissue replacement (73,p270)[77]

Poly (alpha amino acids)

Burns[62]

Skin grafting[62]

Polyesters

Burns[62]

Chest wall mesh[62]

Knit arterial replacement[63]

Mesh for diaphram[62]

TABLE 2 (CON'T)

POLYMER USES IN MEDICINE

Polyesters (con't)

Scleral buckling[62]

Skin replacement[62]

Tendon repair[62]

Polyethers

Dental impression materials[64]

Drug carriers[60]

Poly(ether urethane ureas)

Artificial hearts[57]

Blood vessel prosthesis[57]

Intraaortic balloon assist device[57]

Polyethylene

Arterial aneurysms[62]

Artificial joints[57,63]

Catheters[62]

Chest wall mesh[62,63]

Containers[62]

Contraception devices[85]

Dural substitute[62]

Gastroscopy[62]

Hernia repair[62]

Hip replacement[85]

Intermedullary plug[85]

Mesh to repair diaphram[62,63]

Nerve repair[62]

TABLE 2 (CON'T)

POLYMER USES IN MEDICINE

Polyethylene (con't)

Orbital flooring[71]

Otological implants[63,85,86]

Pleural cavity prosthesis[62]

Scleral buckling[62]

Sinus implants[62]

Skin grafting[62]

Soft tissue replacement[77]

Sutures[62]

Tendon repair[62,85]

Testes[62]

Used as a Standard of Comparison in the Toxicity of Biomaterials[63]

Polyformaldehyde

Soft tissue replacement[77]

Poly(lactic acid)

Controlled drug release[59,87]

Fibers[87]

Microcapsules[87]

Polypropylene

Arterial replacement[62]

Chest wall mesh[62]

Mesh for diaphram repair[62]

Polyolefins

Blood pump components[88]

Filters for blood[83]

TABLE 2 (CON'T)

POLYMER USES IN MEDICINE

Polyolefins (con't)

Finger joints[63,85]

Hammersmith mitral valve prosthesis[85]

Sutures[85]

Polyoxyethylene Sorbitan Monolaurate

Bound enzyme substrate[69]

Polystyrene

Soft tissue replacement[77]

Polysulfides

Dental impression materials[64]

Polysulfones

Heart valve components[63]

Medical instrumentation[63]

Neurological implants[63]

Pacemaker components[63]

Soft tissue replacement[77]

Poly(vinyl alcohol)

Burns[62]

Dural substitute[62]

Hernia repair[62]

Joint replacement[75]

Skin replacement[62]

Poly(vinyl chloride)

Catheters[62]

Containers[62]

TABLE 2 (CON'T)

POLYMER USES IN MEDICINE

Poly(vinyl chloride (con't)

Soft tissue replacement[77]

Synthetic ligatures[62]

Tubing[62]

Urethra-gastric intubation[62]

Poly(vinyl pyrrolidone)

Plasma substitute[83]

Poly(vinyl sulfonic acid)

Anticoagulant[69]

Silicones

Aneurysms[62]

Aortic balloon assist devices[89]

Arterial replacement[62]

Artificial heart valves[69,89,90]

Artificial heart walls[62]

Augmentation and restoration of genetilia[63]

Breast augmentation[63,90]

Breast replacement[91]

Burns[62]

Burr hole cover[68]

Catheters[62,81,90]

Contact lens[65]

Controlled drug delivery[63,92]

Corneal replacement[62]

Dental impression materials[64]

TABLE 2 (CON'T)

POLYMER USES IN MEDICINE

Silicones (con't)

Ear restoration[62]

Electronic pacemakers[62,63,89]

Facial reconstruction[63]

Finger joint replacement[63,90]

Hydrocephalus shunts[68,90]

Kidney dialysis equipment[93]

Lens replacement[62]

Nerve repair[62,90]

Neurostimulator leads[63]

Opthamological prosthesis[63]

Orbital flooring[71]

Outer ear replacement[86]

Oxygenating membrane[79]

Plastic surgery[63]

Pleural cavity prosthesis[62]

Prostheic patch grafts[89]

Retinal detachment[62,65,71]

Rhinoplasty[62]

Sheath for neurorhaphy[68]

Skin replacement[62]

Small joints[57]

Soft tissue replacement[57,63,77]

Tear duct[62]

Tendon replacement[62,63]

TABLE 2 (CON'T)

POLYMER USES IN MEDICINE

Silicones (con't)

Toe joint replacement[63,90]

Tubing[62,81,89]

Urethra[62,63,90]

Urinary bladder[62]

Uterus[62]

Wrist joint replacement[63,90]

Silk

Sutures[62,80]

Teflon

Aneurysms[81]

Arterial replacement[57,62,63,81,94]

Bile duct[62]

Catheters[62]

Coating electrodes[68]

Diaphram[62]

Dural substitute[62,94]

Ear reconstruction[62]

Gastroscopy[62]

Heart valves[94]

Hernia repair[62]

Maxillofacial prosthesis[63,94]

Nerve repairs[62]

Nose reconstruction[62]

Orbital flooring[71]

TABLE 2 (CON'T)

POLYMER USES IN MEDICINE

Teflon (con't)

Orthopedic prosthesis[63]

Otological prosthesis[63,94]

Plastic surgery[63]

Pleural surgery[63]

Retinal detachments[71]

Soft tissue replacement[77]

Sutures[94]

Ureters[62]

Valve in hydrocephalus shunt[94]

Vein replacement[57,63,81,94]

Urethanes

Artifical heart components[67,95]

Atificial kidney components[67,95]

Blood bags[95]

Blood vessels[95]

Bubble trap units[67]

Catheters[95]

Endotracheal tubes[95]

Facial restoration[95]

Heart assist devices[67,95]

Insultation of intravenous lead for pacemakers[63]

Nerve repairs[62]

Roller pump segments[67]

Soft tissue replacement[77]

TABLE 2 (CON'T)

POLYMER USES IN MEDICINE

Urethanes (con't)

Solution containers[95]

Surgerical prosthesis[95]

Treatment of hypercholesterolemia[69]

Tubing[67,95]

TABLE 3

OBJECTIVES OF DESIGN TO CHEMOTHERAPEUTIC POLYMER DRUG SYSTEMS

1. To lower toxicities and diminish side effects.[1,2,31,50,96,97,98,99,100]
2. To increase the activity of the drug.[1,101]
3. To increase specificity of drug treatment.[1,2,31,92,97,98,101]
4. To prolong duration of drug activity.[1,2,31,60,97,98,100,101,102,103,104]
5. The drug should have a wide concentration range of biological activity.[101]
6. The drug should have good variablility and specificity for the target cells.[1,101]
7. The amount of drug agent required for the desired effect should be decreased.[2,50,100]
8. A lessened frequency of dosing should be achieved.[50,100]
9. Patient participation should be minimal.[92,100,104]
10. Highly skilled personnel should not be needed in its application[100,104]
11. The system should be easily and reproducibly produced as a pure material.[62,77,99]
12. The system should undergo needed hanges in shape without being degraded or adversley changed.[62,77,99]
13. The needed chemical, physical, and mechanical roperties should be met for performing the designed function.[62,77,99]
14. The system should not induce thrombogenisis or interfere with normal clotting when in contact with the blood.[77]
15. The system should not alter the configuration or stability of cellular or blood components.[62,77,105]
16. The system should not induce inflammatory or foreign body reactions.[62,77,105]
17. The system should not be carcinogenic.[62,77,105]
18. Surrounding tissue should not modify it.[105]
19. Single, rather than combination, drug therapy should be achieved.[92]

then homopolymerize or copolymerize it, or 3) to place the drug in the polymer matrix and allow it to diffuse out into the biological fluids.[1,2] These designs are used in one of two systems: a reservoir system where the drug forms a core surrounded by the polymeric excipient, or a monolithic system where the drug is dispersed (or somtimes dissolved) in the polymer matrix.[58] The drug moiety in the bonded systems comes from the synthesis of a polymerizable drug derivative capable of interacting with other synthetic monomers, the synthesis from natural active macromolecules, or the interaction of known drugs with synthetic monomers of polymers.[1]

Physical forms of controlled release systems include microcapsules or pellets that are implanted; microcapsules or microparticles that are injected; envelopes, films or laminates that are placed in the cul-de-sac of the eye, oral cavity, or subcutaneously; various ring and T-shaped intravaginal and intrauterine devices; and bandages for topical and transdermal delivery.[58] A limited solubility polymer can be implanted or injected in the body and function for long periods of time. This then releases the drug slowly, so that less diffuses away from the target site, raising the therapeutic index of the drug.

An example of a reservoir system on the market today is Progestasert^{R}, an intrauterine device that delivers progesterone at a constant rate to the uterus for 1 to 3 years for contraception. A monolithic system available for a delivery of pilocarpine for 1 week in the treatment of glaucoma is Occusert^{R}, an ocular therapeutic system which delivers the drug at a constant rate.[50,51] Artificial tears in solution form and scopolamine, a motion sickness drug delivered through

the skin by a transdermal system, are also available. Nitroglycerine is also available in 24 hour transdermal patches.[100]

Several problems are encountered when polymers are used in the body. To quote Lee, "In this internal environment, dynamic responses continually interplay to fight off anything that doesn't seem to belong there, with an implacable dedication to devouring, destroying, or completely isolating what the polymer chemist and surgeon or physician hopes will satisfactorily replace a deficient organ or repair and sustain or augment the function of a part of the body."[106] Lee also says, "In those applications not involving contact with flowing blood, the principal problems encountered have been inflammatory reactions, fibrotic responses, the rejection of superficial implants, and to some extent, chronic intractable infections."[91] Four stages of polymer degradation in the body have been identified: 1) Hydration – disruption of van der Waals forces and hydrogen bonds, 2) Strength Loss – initial cleavage of backbone covalent bonds, 3) Loss of Mass Integrity – further cleavage of covalent bonds to polymer molecular weight levels insufficient for mass coherence, and 4) Mass Loss – dissolution of low molecular weight species and phagocytosis of small fragments.[99] TABLE 4 lists other problems encountered in treatment involving polymers.

Sometimes biodegradation in the body is not a problem, especially in systems utilizing this phenomenon in controlled release such as a time release capsule.[107] These types of systems take advantage of the natural action of the body in removing foreign objects from itself. Biodegradable polymers are made from polyamino acids, polyvinyl alcohol derivatives, α-polyesters, α-polyester homopolymers, polysaccharide derivatives,

TABLE 4

PROBLEMS WITH POLYMER USE

1. Thrombogenesis.[69]
2. Tissue incompatibility.[69,77,100]
3. Maintenance of chemical and mechanical integrity of materials in contact with the body fluids.[69]

Tissue irritation.[69]

Fibrous capsule formation.[82]

Infectious susceptibility.[82]

Thermal necrosis and monomer migration with *in situ* curing.[76]

8. Low mechanical strength compared to metal and ceramics.[61,77]

Biodegradation.[61,100]

10. Impurities.[61]
11. Hypersensitivity of patients.[67]
12. Allergic reactions.[67]
13. Inflammatory response.[67]
14. Leeching of plasticizers.[67]
15. New physiological toxicities due to high molecular weight of material.[102]
16. Surgery is needed for implantation.[100]
17. Pain caused by implant.[100]
18. Expense of system.[100]
19. Adequate safeguards against overdose.[100]
20. Difficulty in shutting off release if necessary.[100]

collagen, and gelatin.[99] Yolles, Eldrige, and Woodland investigated a biodegradable polymer containing a drug and found that if the drug is leached from the surface of the polymer, a more constant level of drug can be released to the patient.[104] Yolles has also studied the release of cyclazocaine, naloxone, and maltrexone (narcotic antagonists); progesterone (a fertility control drug); and cytoxin and ~~cis~~-dichloro-diaminoplatinum (two anticancer agents) from poly(lactic acid) composites.[59] Other researchers have used this approach with anticoagulants and depressant delivery systems.[87]

Whitely, Chu, and Galvan found that higher and more prolonged serum concentrations and decreased rates of secretion of methotrexate occurred when methotrexate was covalently bound to bovine or murine serum albumin, bovine IgG, chymotrypsin, or various molecular weight dextrans and then injected intraperitoneally into BDF mice. This leads to an increased life span when used on certain types of cancer cells, each carrier enhancing the drug's effectiveness in a specific way on a specific type of cell. Other carrier bound systems already investigated include DNA containing adriamycin or daunomycin, lipid vesicles containing actinomycin D or cytosine arabinoside, and antibodies with chlorambicil or N,N-bis-(2-chloroethyl-p-phenylenediamine attached.[41]

Release of drugs from microcapsules can occur through a diffusion process which consists of: 1) water permeating the coating, 2) an aqueous solution of the water soluble drug is formed within the structure, and 3) then this drug solution diffuses through the coating. The release rate is a function of the permeability of the film to water, the solubility of the solid, and the permeability of the film to the saturated solution.[107]

Poly(hydroxyethyl methacrylate) has been used by Levowitz and coworkers in drug delivery systems by utilizing its absorptive properties. The polymer was charged by absorption by the dried polymer, admixing at the time of polymerization, or by placing the drug in solution with the polymer.[72] Yoshida, Kumakura, and Kaetsu have reported on diffusion of KC1 out of polyacrylates and polymethacrylates polymerized at low temperatures with the KC1 dispersed throughout at the time of polymerization. The goal they had in mind was to treat hypopotassemia with such a system. The release of the drug was found to occur in three stages: 1) Quick release caused by quick dissolution of KC1 from the surface of the polymer due to swelling by water, 2) a stationary state during release through the matrix, and 3) release rate decrease due to starvation of the polymer in the matrix. They found that the more hydrophilic the matrix, the faster the release rate of the drug. Also, the release rate of KC1 increased linearly with the square root of time (Higuchi kinetics) and increases proportionately to the water content which increases drug diffusion.[108,109] This group also studied the release of entrapped enzymes from the same type of polymers and found the pH can have an effect on drug releases. "The polymer matrices produced by this method were characterized in porous structure due to crystallized solvent or crystallized water in the matrix at low temperatures; this porous structure facilitates substrate or drug diffusion in and out of the matrix."[110]

Controlled drug dissolution by polymer entrapment is attractive due to the durable and moderately controlled pharmaceutical effects which can be achieved. The polymeric agent might be implanted or suspended in the affected organ to treat that organ more specifically. This

specificity would be due to the reduced mobility and slow release of the drug and reduce its side effects.[97,110]

Another approach is to attach the drug unit directly to a polymer by covalent bonding. There are three types of polymers where the drug group is covalently bound in the polymer. The first type is the insoluble polymeric drugs which are good for easily accessible sites and controlling the release of drugs over a long period of time. These are like the controlled release systems. However, they are undesirable for treating internal organs or widespread disease because of the need for surgical implantation or injection and the localized treatment they give. The second type is soluble polymeric drugs which are good for administration orally or by injection. They require no surgery, and have versatility in copolymerization to impart solubility and specificity to the polymer. These simple soluble polymers have the drawback in lack of complete specificity for target cells and that their high molecular weight may exclude the drug from entering certain parts of the body. The third type is directed soluble polymeric drugs. These are more complicated in that they are composed of three parts: 1) the therapeutic agent, 2) a solubilizing unit, and 3) a directing unit. These would zero in on the target cancer cells and have minimal effect on other parts of the body. As Gebelein states, "The directing units could be another monomer, such as a sulfonamide type, or a biological unit, such as an enzyme, protein, nucleic acid, or some related species."[32] These "guided missile" polymeric drugs have a great potential for highly specific action.[2,32,41.,73]

Several investigators have synthesized polymers containing an active unit in backbone which was then attached to a monomer or polymer matrix or was encapsulated by a polymer membrane.[1]

Various Polymeric Drug Systems

Several examples of polymeric drug systems are cited in the literature. Ascolf, Casini, Ferappi, and Tubaro have prepared many polymers containing antibacterial drugs exhibiting antibacterial actions.[102] Because the major shortcoming of radioprotective agents is their short half-lives or protection, Overberger *et al* prepared a polymer in which a protective moiety is released slowly by the polymer to which it is attached. This polymer has been shown to be effective in rats.[111] Synthetic copies of natural hormones and enzyme analog have been prepared. Some synthetic endorphins and enkephalins have over 850X the analgesic action of morphine and over 28,000X the activity of natural methionine enkephalin.[57] A sulfa drug has been attached to the polymer backbone in N'-(4-sulfonamidophenyl)-iodourea.[112] Antisilicosis activity is shown by poly(2-vinylpyridine)-1-oxide. A thiol containing polymer prevents mercury reabsorption in the intestines of rats.' A copolymer of procaine and polyethylene glycol achieved longer duration of the drug.[60] Short copolymers of dimethylolurea-sulphonamide or dimethylolureasulphone proved useful as antimalarial drugs.[113] Some copolymers of N'-acylsulfanilamide-formaldehyde are more effective antimalarial drugs than the monomer.[114] Time-release tablets containing quinine sulfate were prepared by Choulis and Papadopoulos.[115] Because of the unpleasant taste and odor of Clofibrate, a liquid hypocholesterolemic agent, it was encapsulated.[116] Chien *et al* studied the *in vitro* and *in vivo* correlation of release rates of ethyndiol diacetate and norgestomet from polymeric devices.[117,118] Mason, Thies, and Cicero studied the release of cyclazocine, and narcotic antagonist, from dl-poly(lactic acid) micro-

capsules *in vitro* and *in vivo*. They found slower release rates from larger capsules.[119]

Clinical trial show Hydro^{R}-coated catheters are effective in preventing infection as opposed to uncoated latex controls.[120] Hydron^{R} has also shown itself effective as an antibacterial coating in suture materials.[121] Abrams and Ronel have prepared a Hydron^{R} device for the zero-order release of cyclazocine. They found the release rate could be controlled by proper geometry, copolymer composition, concentration of ionogenic groups, and crosslink density. These devices have been tested for periods approaching one year.[122] The sustained release of naloxone was studied from a biologically inert and non-degradable polymer by Fishman, Hahn, Norton, Ronai, and Foldes. They found the system to be active for 29 days.[123]

Release of nitrofurantoin, nitrofurazone, oxytetracycline, and tetracycline from gelatin capsules containing one of three diluents and with or without a lubricant and wetting agent was studied by Newton and Razzo. They found that the type of drug, type of diluent, level of diluent, and lubricant each effect drug release, but the wetting agent did not.[124] The use of gentamicin in poly(methyl methacrylate) bone cement was found to deliver localized bacteriocidal action in dogs. Gentamicin activity in this system was shown for over 70 weeks testing *in vitro*. The release rate was found to be dependent on the shape and size of the system, the gentamicin content of the system, the amount of elution liquid, the period of contact, and the procedure followed.[125,126]

Several polymeric drug delivery systems have been cited in the literature. The cyclopolymer of 1-vinyluracil has shown inhibition of

the murine leukemia virus.[127,128,129,130,131] The toxic level of poly(1-vinyluracil) was found to be 1mM, but only in growing and dividing cells. It is non-toxic to stationary cells.[32,96,132,133] Poly(9-vinyladenine) has been shown to inhibit E. Coli RNA polymerase and is anti-viral.[130,131,135]

Actinomycin is a polypeptide used in the treatment of Hodgkin's disease and lymphosarcoma. A naturally occuring polysaccharide, Statolon, is active against mouse leukemia[2.2] The 9-α-fluorocorticoids are used in treatment of some neoplasms of lymphoid tissue where they inhibit the incorporation of precursors of purines innucleic acid synthesis, and the incorporation of formate into DNA.[5]

Methacryloxytropone polymers have shown greater neoplastic activity than their corresponding monomers.[73,135] Weiner, Lahan, and Zilkda prepared polymeric phenethylamines which showed a long lasting activity with reduction in side effects.[2] Alternating 1:2 divinyl ether: maleic anhydride copolymer ("Pyran") exhibits antitumor activity against Ehrlich and Lewis lung cancer in mice.[17] Fractions of narrow molecular weight range of this type of polymer have advantages over those which are polydisperse, in that the higher the molecular weight, the greater their toxicity in tumors.[2,136] Poly(sodium acrylate) has shown promise against intramuscular Walker carcinoma 256 of the rat. It showed antitumor activity against solid tumors, but not against ascites cells.[136] However, many polyanionic polymers that have exhibited anti-neoplastic activity are too toxic for in vivo use.[73,137] Some polymers are capable of inducing interferon production, and some interferons have antineoplastic activity.[73]

Besides 5-FU, other cancer chemotherapeutic agents which have been attached to polymer chains include aziridine derivatives, cyclophosphamides, and 5-methyl-2-phenyl-1,3-dioxyboriman-5-ylmethyl methacrylate.[98] Phenylethylamine, dl-amphetamine, 1-ephedrine, and tyramine have been attached to both poly(methacrylic acid) and starch.[103]

5-Fluorouracil

The properties of 5-FU make it useful for cancer chemotherapy. The fluorine at position 5 causes the hydrogen on N-3 to have a lower pKa than uracil.[14,18,44] Del Bene has calculated the stabilization energies of water-5-FU complexes using ~~ab initio~~ SCF and SCF-CI calculations with the STO-3G basis set. These calculations confirmed 5-FU to be a better proton donor to water than uracil, especially through the N-3 group.[138] In solution, the mono-anionic form exists as one of two tautomeric forms depending on the dielectric constant of the solvent.

Like unsubstituted uracil, 5-FU can undergo addition reactions across the double bond, with subsequent ring opening reactions. Palladium/carbon catalyst in sodium hydroxide allows hydrogenation of the C-F bond, and polarographic reduction about pH 7.4 yields 5,6-dihydrouracil. Hydrolysis of the fluorine occurs in basic solutions. The fluorine at position 5 makes the oxygen at position 4 susceptable to nucleophillic attack compared to the oxygen at position 2, enabling preferential reaction to occur at carbon 4. The nitrogens in 5-FU are also subject to reaction by appropriate reagents. Unsaturated reagents react at N-1 and saturated react at N-3.[18,44]

Several researchers have tried to modify 5-FU to increase its therapeutic index. Two approaches have been taken to achieve this goal:

1) preparing derivatives of 5-FU by adding various groups on the ring, and 2) by incorporating the drug moiety into a polymer. TABLE 5 lists position 4 susceptible to nucleophillic attack compared to the oxygen at position 2, enabling preferential reaction to occur at carbon *4*. The nitrogens in 5-FU are also subject to reaction by appropriate reagents. Unsaturated reagents react at N-1 and saturated react at N-3.[18,44]

Several researchers have tried to modify 5-FU to increase its therapeutic index. Two approaches have been taken to achieve this goal: 1) preparing derivatives of 5-FU by adding various groups on the ring, and 2) by incorporating the drug moiety into a polymer. TABLE 5 lists members of the first group with their corresponding structures and TABLE 6 lists members of the second group with their structures.

Derivatives of 5-fluorouracil

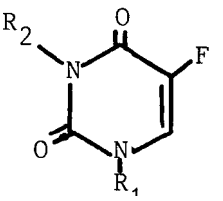
Hillers, Zhuk, and Lidaks prepared 1-(2'-furanidyl)-5-fluorouracil (Structure I Table 5) in 1967. Hiller, Zhuk, Lidaks, and Zindermane then prepared 1-(2'-pyranidyl)-5-fluorouracil in 1972. Each of these compounds was found to be less toxic than 5-FU itself.[44]

In 1972, Meiren and Belousova found that 1-(2'-furanidyl)-5-fluorouracil (also called fluorofur) is a weak inhibitor of de novo synthesis of thymine and ribose pyrimidines in mouse tumors in vitro. Its action was thought to come from the hydrolysis and subsequent release of 5-FU from the molecule, making fluorofur a simple transportation form of 5-FU.[139]

Nesnow, Miyazaki, Khwaja, Meyer, and Heidelberger in 1972 studied several pyridine nucleosides related to 5-FU and thymine. Among these were 2,4-dimethyoxy-5-fluoropyridine, 4-hydroxy-5-fluoro-2-pyridone,

TABLE 5

5-FLUOROURACIL DERIVATIVES



Basic Structure

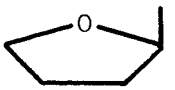
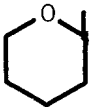
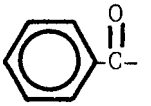
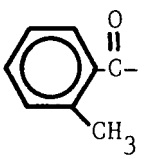
Structure	Nomenclature	R_1	R_2	Ref
I	1-(2'-furanidyl)5-FU		H-	*44,139*
II	1-(2'-pyranidyl)-5-FU		H-	44
III	1-acetyl-5-FU	$CH_3-\overset{O}{\overset{\|}{C}}-$	H-	48
IV	1-benzoyl-5-FU		H-	48
V	1,3-dimethyl-5-FU	CH_3-	CH_3-	48
VI	1-allyl-5-FU	$CH_2=CH-CH_2-$	H-	48
VII	1-butenyl-5-FU	$CH_3-CH=CH-CH_2-$	H-	48
VIII	carboethoxymethyl-5-FU	$C_2H_5-O-\overset{O}{\overset{\|}{C}}-CH_2-$	H-	48
IX	acetoxyethyl-5-FU	$CH_3-\overset{O}{\overset{\|}{C}}-O-CH_2-CH_2-$	H-	48
X	1-O-toluyl-5-FU		H-	48

TABLE 5 (CON'T)

5-FLUOROURACIL DERIVATIVES

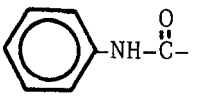
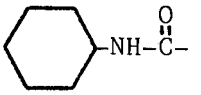
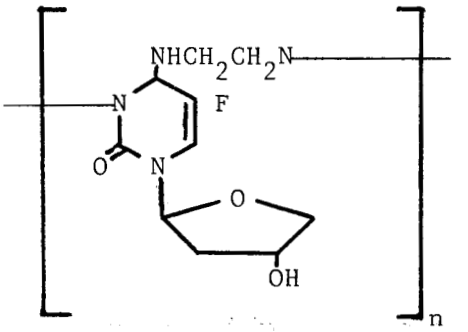
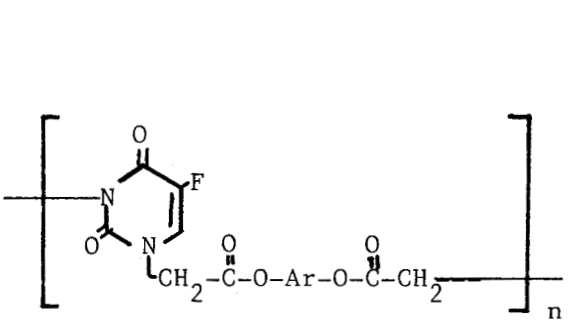
Srtucture	Nomenclature	R_1	R_2	Ref
XI	methylcarbamoyl-5-FU	$CH_3-NH-\overset{O}{\overset{\|\|}{C}}-$	H-	142
XII	ethylcarbamoyl-5-EU	$CH_3-CH_2-NH-\overset{O}{\overset{\|\|}{C}}-$	H-	142
XIII	isopropylcarbamoyl-5-FU	$CH_3-\overset{CH_3}{\overset{\|}{C}}H-NH-\overset{O}{\overset{\|\|}{C}}-$	H-	142
XIV	phenylcarbamoyl-5-FU		H-	142
XV	cyclohexylcarbamoyl-5-FU		H-	142
XVI	1-hexylcarbamoyl-5-FU	$C_6H_{13}-NH-\overset{O}{\overset{\|\|}{C}}-$	H-	143
XVII	5-fluoro-N'-(N-ethylcarbamoyl)uracil	$CH_3-CH_2-NH-\overset{O}{\overset{\|\|}{C}}-$	H-	37,97 98,144
XVIII	5-fluoro-N'-(N-allylcarbamoyl)uracil	$CH_2=CH-CH_2-NH-\overset{O}{\overset{\|\|}{C}}-$	H-	37,97 98,144
XIX	5-fluoro-N'-(N-isopropylidene-carbamoyl)uracil	$CH_2=\overset{CH_3}{\overset{\|}{C}}H-NH-\overset{O}{\overset{\|\|}{C}}-$	H-	37,97 98,144
XX	5-fluoro-N'-(N-vinylcarbamoyl) uracil	$CH_2=CH-NH-\overset{O}{\overset{\|\|}{C}}-$	H-	37,97 98,144
XXI	1-(2-carbomethoxy-acryloyl)-5-FU	$CH_3-O-\overset{O}{\overset{\|\|}{C}}-CH=CH-\overset{O}{\overset{\|\|}{C}}-$	H-	17

TABLE 6

POLYMERS CONTAINING 5-FLUOROURACIL

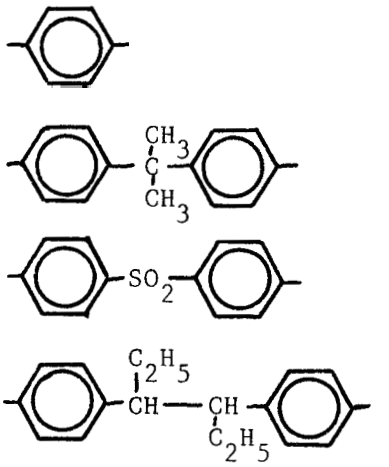


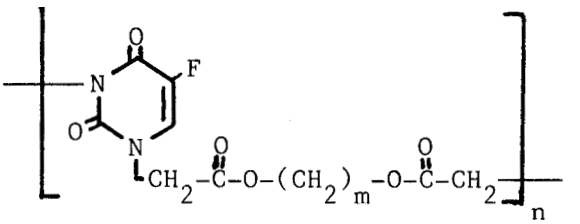
Structure I- Polymer prepared by Ballweg *et al.*98



(II)

Ar=



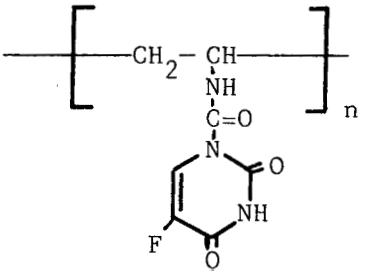


(III)

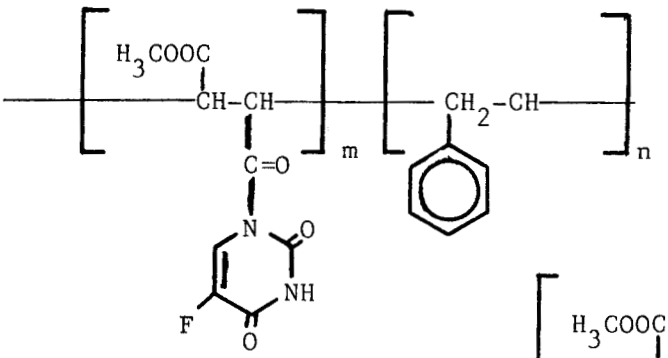
Structures II and III– Polymers prepared by Butler *et al.*17,73

TABLE 6 (CON'T)

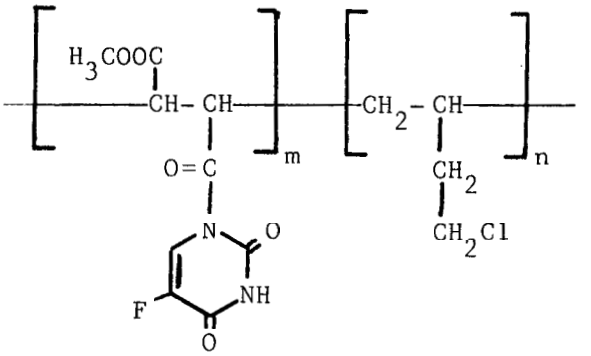
POLYMERS CONTAINING 5–FLUOROURACIL

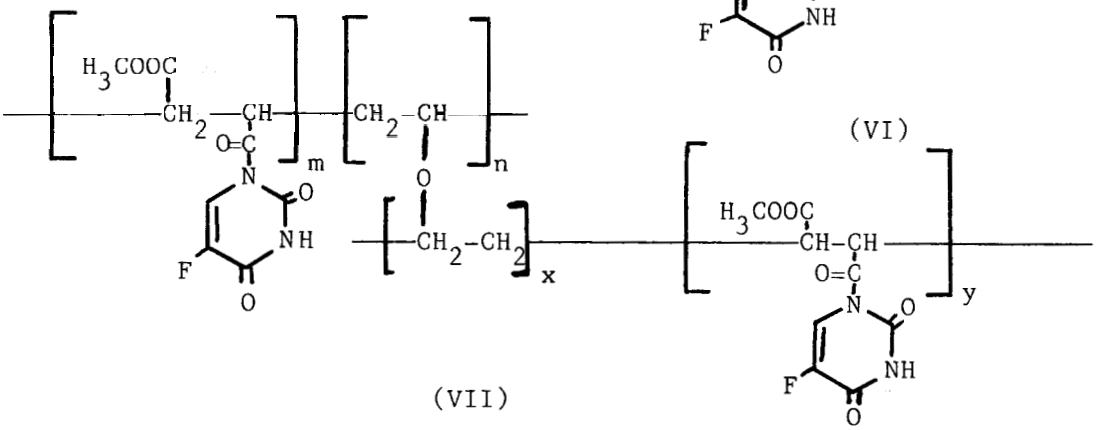


Structure IV– Polymer prepared by Gebelein et al.[73,97.98]



(V)





(VI)

(VII)

Structures V through VII– Copolymers prepared by Butler et al.[17,73]

4-hydroxy-5-fluoro-1-(2,3,5-tri-O-benzoyl-α-D-ribofuranosyl)-2-pyridone, 4-hydroxy-5-fluoro-1-(α-D-ribofuranosyl)-2-pyridone, 2-hydroxy-5-fluoro-1-(α-D-arabinofuranosyl)-4-pyridone($O^{2}\rightarrow 2'$)-cyclonucleoside, and 4-hydroxy-5-fluoro-1-(2-deoxy-α-D-erythro-pentofuranosyl)-2-pyridone. None of these compounds was found to inhibit any of several cell lines in culture.[140]

Okada, Nakayama, and Mitsui reported in 1974 on several derivatives of 5-FU. They produced 1-acetyl-5-FU, 1-benzoyl-5-FU, 1,3-dimethyl-5-FU, allyl-5-FU, butenyl-5-FU, carboethoxymethyl-5-FU, acetoxyethyl-5-FU and 1-O-toluyl-5-FU.(Structures III-X, Table 5). Of these,. it was found that 1-acetyl-5-FU and 1-benzoyl-5-FU were superior to 5-FU in both effectiveness and lowered toxicity *in vivo*. The first hydrolyzes readily in water, and the second in hydrophobic media.[48]

Fujii, Okuda, Toide, *et al* studied the pharmokinetics and metabolism of 1-(2-tetrahydrofuryl)-5-fluorouracil in rats in 1974 and found the blood levels were higher and more continuous with this than with 5-FU. They also found the uptake of each was the same in tumor as it was in the other tissues, except in the liver and kidney, where uptake was higher.[141]

Hoshi, Iigo Yoshida, and Kuretami synthesized 1-carbamoyl derivatives of 5-FU in 1975 which were more activeand less toxic than 5-FU or 1-(2-tetrahydrofuryl)-5-fluorouracil by oral administration These derivatives were methylcarbamoyl-5-FU, Ethylcarbamoyl-5-FU, isopropylcarbamoyl-5-FU, phenylcarbamoyl-5-fluorouracil, and cyclohexylcarbamoyl-5-FU. (Structures IX-XV, Table 5). The later of these was most effective.[142]

Hoshi, Iigo, Nakamura, Yoshida, and Kuretani then synthesized and studied 1-hexylcarbamoyl-5-FU (Structure XVI, Table 5) in 1976.

This compound has a higher therapeutic index than 5-FU or 1-(2-tetrahydrofuryl)-5-FU when treating Nakahara-Fukuoka sarcoma and adenocarcinoma-755 by oral administration. 1-Hexylcarbamoyl-5-FU was also active against solid and ascites tumors. It was markedly active against ascites sarcoma-180 and was moderately active against Ehrlich ascites carcinoma. The compound has a wider tumor spectrum than 5-FU or 1-(2-tetrahydrofuryl)-5-FU by oral administration.[143]

Gebelein and Morgan reported on the synthesis of 5-fluoro-N'-(N-ethylcarbamoyl)uracil, 5-fluoro-N'-(N-allylcarbamoyl)uracil, 5-fluoro-N'-(N-isopropylidenecarbamoyl)uracil, and 5-fluoro-N'-(N-vinylcarbamoyl)-uracil.(Structures XVII-XX, Table 5). The last three were potentially polymerizable. The allylic derivative did not polymerize, as is typical for this class of compound. The acryloyl derivative hydrolyzed too rapidly to be of interest.[37,97,98,144] Further research by Gebelein and Ryan revealed that the hydrogen bonding solubility parameter had effect on reaction yields. The higher the δ_H, the higher the yield. This is consistent with the proposed mechanism of reaction presented in earlier papers. The resulting monomer interacted with the solvent to a lesser extent as was expected and this was shown by the decreased solubility as compared to 5-FU, but the increased solubility shown in poor solvents for 5-FU.[144]

Umrigar, Ohashi, and Butler made 1-(2-carbomethoxyacrylol)-5-FU (Structure XXI, Table 5) in 1979. This monomer hydrolyzed too rapidly to be of practical use.[17]

Polymeric Systems Containing 5-Fluorouracil

The first polymer containing 5-FU was produced by Ballweg et al and is reported to have biological activty.[98] Further work has

been reported on similar polymers.[145,146] (See Structures I-III, Table 6).

Gebelein *et al* have synthesized and studied poly[5-fluoro-1-(N-vinylcarbamoyl)uracil]. This polymer was easily prepared by free radical polymerization and has shown activity against P38 leukemia by releasing 5-FU slowly [73,97,98] (See Structure IV, Table 6).

Umrigar, Ohaski, and Butler have copolymerized 1-2-carbomethoxyacryloyl-5-FU with styrene, divinyl ether, and 2-chloroethyl vinyl ether. These copolymers hydrolyze more slowly than the monomer, but the homopolymer hydrolyzes too rapidly to be of practical use. The copolymers show some antineoplastic activity against P388 leukemia using CD_2F_1 mice, presumably due to the slow release of 5-FU. The survival times for animals treated increased over that of controls to the following extent: 1) St/CMAFU-1.92X, 2) DVE/CMAFU-1.89X, 3) CEVE/CMAFU-1.65X. They found the hydrophobic character of the polymer and the strength of the bond to 5-FU are very important in decreasing the rate of hydrolysis (See Structures V-VII, Table 6).

It is interesting to note that carbamate and amide linkages are expected to hydrolyze slowly in the body providing controlled levels of drug release according to other studies as well. Polymers containing such linkages have been found to undergo slower hydrolysis than their corresponding monomers and showed a greater duration of activity along with lower toxicities than the monomers.[103]

Yoshida, Kumakura, and Kaetsu have studied the release of 5-FU from polymers containing an adsorbent and prepared by radiation induced polymerization at $-78^{o}C$. Activated charcoal, molecular sieves 4A, activated clay, and silica gel were used as adsorbents. They found as the

concentration of an adsorbent increased, the release rate of 5-FU decreased. They had also demonstrated in previous studies that the release rate of drugs "could be controlled by various methods, such as the increase of the hydrophilicity of the matrix, the addition of soluble polymer, and the addition of pore making components." In this study, they showed that 5-FU is released from a hydrophobic matrix much faster than a hydrophilic matrix. The release rates of 5-FU from these matricies followed Higuchi kinetics.[147]

Kaetsu, Yoshida, and Yamada studied the release of entrapped 5-FU from composites of various shapes – rods, tablets, membranes, and powder. The matrix was poly(diethylene glycol diemthacrylate) [including a small quantity of poly(styrene, poly(vinyl formal), poly(vinyl acetate), or poly(methyl methacrylate) and polyethylene glycol #600] polymerized at low temperature with radition. The release rates from the matrices depend on the kind of polymer and monomer concentration in polymerization and on the shape of the composite. The kind and amount of added polymer changed the hydrophilic nature of the composite. As the hydrophilic nature of the composite decreased, so did the diffusion rate of the 5-FU from matrix. The release rate decreased according to the shape of the composite in the following order: powder, membrane, tablet, sphere. These systems followed Higuchi kinetics in their release of 5-FU. Nevertheless, these studies show that release rate can be controlled by the hydrophilic nature and shape of the composite.[148]

Research has also been done on attaching 5-FU to various polynucleotides.[149]

Drobnik, Spacek, and Wichterle have studied the permeation of 5-FU across membranes prepared from hydroxyethyl methacrylate and butyl

methacrylate. They found the rate of dilution can be slowed by increasing the hydrophobicity of the matrix (increasing the percentage of butyl methacrylate in the membrane), by using a thicker membrane, or by using a more dilute solution of drug. When the percentage of butyl methacrylate reached 20% in the membrane, diffusion practically stopped.[151]

Levowitz, LaGuerre, Calem, Gould, Scherrer, and Schoenfeld have charged Hydron with 5-FU by placing a crosslined disc in a 0.5% 5-FU solution for five days. These discs were then placed in 0.1 M phosphate buffer or human plasma. Release of 5-FU occurred rapidly in the first 48 hours and progressively declined thereafter. Elution occurred at a much faster rate in the buffer solution than in human plasma.[152]

Arlen, Schener, Cukierman, Nagin, and Levowitz conducted *in vivo* studies using rabbits implanted with a Hydron disc saturated with 5-FU which showed 65% of the agent entered the tissues and body fluids in the first 48 hours. Using CF_1 white mice, they showed pellets of Hydron saturated with 5-FU and implanted into the peritoneal cavity offered protection against Ehrlich's ascites tumor. As a result of these studies, an implantable device was constructed yielding fairly straight line curves for the release of 5-FU *in vivo*. These studies show that selective uptake occurred in those tissues adjacent to the implantable chamber and a marked fall off in uptake by those tissues usually noted to be selectively affected by the drug. This device could be useful in treating sites containing residual tumor tissue in the immediate postoperative period or in patients where radiation therapy had failed or where their vascular system was damaged so that

conventional chemotherapy could not be used. These workers have designed a Hydron device which could be implanted against the tumor by surgery to deliver antitumor agents in localized therapy. The drawbacks to this system include the need for tubes perforating the skin, lack of mobility during treatment, increased patient participation, and the need for professional monitoring of the device.[152]

Biomedical Properties of Acrylic Resins

Acrylic resins were first used in biomedical applications in 1935 when they were patented by ICI and Rohm and Haas. WWII spurred further interest in their use. In 1941, Zander used acrylics to repair cranial defects. This was the first year poly(methyl methacrylate) was reported on by Deichman et al. Acrylics were used as hip endoprosthesis in 1943. Ridley noticed that fragments from acrylic windows lodged in the eyes of pilots were tolerated well and from this the idea of contact and intraocular lenses arose. In the 1950's the "invisible" filling was introduced into the field of dentistry. In 1960, Charnley introduced bone cement for anchoring metallic endoprosthesis.[67]

Various types of reactions to acrylic implants have been observed: 1) TOXIC, SYSTEMIC, or HYPERSENSITIVE where the reaction is provoked by the presence of low molecular weight constituents like monomers, comonomers, catalysts, plasticizers, or the like; 2) TISSUE or HISTOLOGICAL where the reaction is provoked by the physical aspects of the material or due to the presenceof the material over a long time.[67]

Since acrylates are more toxic than methacrylates, more research has been done on methacrylates for biomaterials. For poly-

(methyl methacrylate) an LD_{50} of 2 ml/kg intraperitoneally and 6 mg/kg subcutaneously was determined from experiments with rats, guinea pigs, and dogs. Homsy reported an LD_{50} value of 1.3 ml/kg for intravenous injection into dogs in 1969. In 1972, Lawrence *et al* found the LD_{50} for intravenous injection into mice to be 0.9 to 1.3 g/kg. The cause of death was ascribed to respiratory failure. This was born out by McLaughlin *et al* in 1973 who observed decreased plumonary function in dogs given a 75 mg/kg intravenous dose. From the study it appeared the lungs were a major exit route for methyl methacrylate from the body, causing them to be the first organ to fail. Liver damage was noted by Spealman in 1945, McLaughlin in 1973, and Holland in 1973. Cardiovascular and pulmonary complications and embolism, sometimes leading to death when bone cement was used in total hip replacement, were reported. This led Charnely, who developed the technique, to investigate the cause of these phenomena. He found the cause to be the technique of the surgeon, and not the cement. Emboli of fat, air, and bone marrow were formed when the cement was forced into the medullary canal, and these emboli then migrated throughout the body causing complications. The blood level of methyl methacrylate in this operation corresponds to a 0.7 mg/kg intravenous dose, the highest level in any type of operation. This level is far below the LD_{50} levels found in animals.[67]

Acrylic resins need improvement in that some residual reaction products are left in the resin, along with various other constituents. The monomer content varies from greater than 1% in opthalmological resins and heat-cured dental prosthesis to about 1-4% in bulk of room temperature cements. Hydroquinone, a stablizier, oxidized to

quinone derivatives, and peroxides, used as inhibitors, are left. Brauer *et al* found 0.75 to 0.80 weight % of peroxide in system which originally contained 1.3 weight %. In cold curing resins, accelerators such as tertiary amines will be partially oxidized to form new contaminants, but some will be left unchanged. All of these constituents can be leached out of the resin during the time it is implanted in the body. It has been established that this leaching causes concentration levels in the surrounding tissues to be well below acceptable levels in the body.[67]

Two problems have been encountered in implanting acrylics in the body: 1) Tissue reactions, mostly foreign body reactions, due to small particles abraded off in mechanically stressed implants, and 2) the reaction of tissues to the high temperature of *in situ* curing of acrylics. Galen and his associates have shown that there is no cause for concern over biocompatability using high purity poly(methyl methacrylate) intraocular implants. The reaction of tissues around the neck of dental implants has been the source of problems in this application.

After acrylic devices have been implanted, they become encapsulated in fibrous connective tissue. The thickness of the capsule and the duration and extent of inflammatory cell infiltration largely depend on mechanical and geometrical factors of the implant. Sharp edges or dynamic mechanical loading are unfavorable. Smooth surface always seems to be covered by a stable interlayer of connective tissue separating it from contacting tissues. Intraocular lenses are contradictory to this in that they are surrounded by soft tissue.

Bacterial infection necessitates the removal of the implant unless treatment by antibiotics is successful. Accoring to Van Mullen, "In the case of cold-curing acrylic resins, antibacterial activity is sometimes attempted by adding antibiotics to cement dough . . . After polymerization the antibiotic compounds appear to be released in locally effective doses. It is believed that an inhibitory concentration can be maintained in the immediate vicinity of the implant up to several weeks after implanation. Accoring to Buchhotz, the antibiotics is still demonstrable even after 2 years." This may be the answer to this problem.[67]

Carcinogenicity has not been reported with use of poly(methyl methacrylate). Tumor formation around implants has been found. Van Mullen observes:

> "Each implanted foreign body can induce malignant degeneration depending on factors such as shape, dimensions, surface roughness, and duration of the implant. The physical nature of the implant is of primary importance, rather than the chemical nature of the material. Tumor formation directly related to implants has only been observed in animals and not in man. Tumor formation in animals is strongly dependant on the nature of the fibrous tissue capsule that is formed around the implant."[67]

This is generally accepted.[67,77]

Interest has increased in porous implant materials such that ingrowth of tissue occurs in them thus achieving a mechanically stable connection between the implant and surround tissues. Various methods are used to achieve porous structures, such as: 1) curing small polymer spheres in molds with a small amount of resin, where pore size is controlled by the size of spheres; and 2) mixing suitable amounts of sucrose or carboxymethyl cellulose gels through the dough. If the pores are large enough, bone or connective tissue will invade the pores.[67]

CHAPTER II

STATEMENT OF THE PROBLEM

Several systems utilizing 5-fluorouracil have been prepared and studied.[17,72,97,102,145,146,147,148,149,150,151,152] However, none of these programs have developed an implantable polymer which is in itself a practical chemotherapeutic medium. Though a few devices have shown promise as constant dose implants, their structure necessitates protrusion of part of the implant through the skin. The causes problems in maintenance of the patient, such as the need for increased precaution against infection. Also, because a constant renewal of the chemotherapeutic solution is necessary as the agent is depleted, the patient would have to remain hooked up to a machine or return frequently for treatment. Both of these options necessitate increased patient involvement and care by highly trained medical personnel.

Matrix encapsulated systems have the drawback in that they cannot be shaped in various ways. There are two polymeric systems which have been reported where 5-FU is attached to a backbone. One is based on the reaction product between 5-FU and fumaroyl chloride. It released 5-FU at too rapid a rate to be of practical value.[17] The other was made by Morgan,[18] but also released 5-FU faster than is desired.[73,97,98]

This study will be concerned with the preparation of a carbamoyl derivative of 5-FU which will then be polymerized and copolymerized with methyl acrylate, butyl acrylate, methyl methacrylate, butyl methacrylate, stearoyl methacrylate, and hydroxyethyl metha-

crylate. The solvent system chosen for this study is 1,4-dioxane since monomer has been found to be very soluble in it. Preparation of the monomer is carried out at room temperature in aluminum foil-covered vessels to prevent light-induced polymerization from occuring. The isocyanate used to prepare the monomer will be isocyanteothylmethacrylate (Figure 3). Triethylamine will be used as the catalyst to facilitate the reaction. Polymerizations will be carried out at 75-80°C in an oil bath and AIBN used as the initiator under a nitrogen atmosphere for 20 hours.

The six comonomers mentioned above will be homopolymerized in the same manner. Two model compounds using piperidine and uracil reacted with isocyantoethylmethacrylate will be made and homopolymerized (Figure 4).

Hydrolysis studies will then be carried out on the 5-FU monomer, its polymer, methyl acrylate copolymers, and butyl acrylate copolymers to determine the relative release and type of release rate of 5-FU from each. Hydrolysis studies on the remaining copolymers is left for future research. The preparation and subsequent study of these 5-FU derivatives may lead to possible antineoplastic compounds.

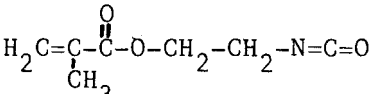
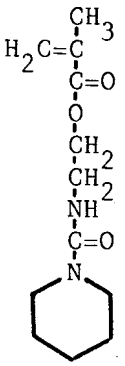
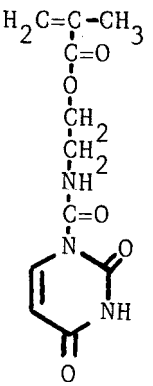


Figure 3- Isocyanatoethylmethacrylate



(a)



(b)

Figure 4 - 1-(N-2-ethylmethacrylcarbamoyl)piperidine (a) and 1-(N-2-ethylmethacrylcarbamoyl)uracil (b).

CHAPTER III

EXPERIMENTAL

Reagents

All reagents used in this study were of practical grade or better. The 1,4-dioxane was passed through activated alumina to remove peroxides before use. The 5-fluorouracil was dried in an oven at 110°C for 72 hours immediately prior to use in preparation of the monomer since isocyanates readily react with water. The acrylates and methacrylates used in copolymerizations were first shaken with a 5% solution of sodium hydroxide to remove the inhibitors present and then dried for 24 hours over $CaCl_2$ immediately prior to use. Table 7 lists the reagents used, their grade, and the manufacturer.

Equipment

All of the glassware used in this study had 24/40 standard taper joints unless otherwise stated. Anhydrous conditions were necessary to prevent interference in monomer synthesis or premature hydrolsis of the monomer or polymer, so all glassware was washed with soap, rinsed with deionized water, rinsed with anhydrous methanol, and then dried at 110°C for 24 hours before use. All products were kept in a desiccator over P_2O_5.

A Buchler flash evaporator was used in evaporating the 1,4-dioxane from the monomer, a Mettler P1000 balance was used to determine the weights of reactants and products, a Cole-Palmer Magna 4 stirring

TABLE 7

Reagents Used

Material	Formula	Grade	Manufacture
α,α' azobisisobutyronitrile	$C_6H_{12}N_4$	Laboratory	Aldrich
Butyl Acrylate	$C_7H_{12}O_2$	Laboratory	Rohm & Haus
Butyl Methacrylate	$C_8H_{14}O_2$	Laboratory	Rohm & Haus
1,4-Dioxane	$D_4H_8O_2$	Reagent	J. T. Baker
5-Fluorouracil	$C_4H_3N_2O_2F$	Practical	P.C.R.
Hydroquinone	$C_6H_8O_2$	Purified	Fisher
Hydroxyethyl Methacrylate	$C_6H_{10}O_3$	Laboratory	Rohm & Haus
Isocyantoethyl Methacrylate	$C_7H_9NO_3$	Experimental	Dow
Methyl Acrylate	$C_4H_6O_2$	Laboratory	Celanese
Methyl Methacrylate	$C_5H_8O_2$	Laboratory	Rohm & Haus
Piperidine	$C_5H_{11}N$	Laboratory	Aldrich
Stearoyl Methacrylate	$C_{22}H_{42}O_2$	Laboratory	Rohm & Haus
Triethylamine	$C_6H_{15}N$	Analytical	Eastman
Uracil	$C_4H_4N_2O_2$	Laboratory	Aldrich

hot plate sustained bath temperature and stirring during the polymerizations, a Beckman Acculab 4 was used for infrared analysis, a Cary 14 spectrophotometer was used for ultra-violet data, a Sargent-Welch IonXChanger Research Model 2 produced the deionized water, a Sargent-Welch control monitored the bath temperature in the hydrolsis studies, and a self-made apparatus described on page 112 was used for studying the hydrolysis of 5-FU.

PROCEDURES

Preparation of 1-(N-2-ethylmethyacrylcarbamoyl)-5-fluorouracil

The procedure for the reaction was the method published by Gebelein.[153]

Into a 500ml Erlenmeyer flask wrapped in aluminum foil, fitted with a calcium sulphate drying tube and magnetic stirring bar, were placed 0.5000g hydroquinone, 0.500ml triethylamine, 20.0000g (0.1538 moles) 5-fluorouracil, 25.00g (0.1611 moles) isocyanatoethyl methacrylate, and 450ml of 1,4-dioxane. The flask was then suspended over a magnetic stirrer and stirred. The reaction (Figure 5) was allowed to proceed for five days, at the end of which time no solid 5-FU was apparent in the flask. The solution was filtered through a Whatman No. 4 filter paper into a weighed 1000 ml round-bottom flask. The dioxane was flash-evaporated at 40 torr and 45°C (113°F). The solid, off-white, crude monomer was dried *in vacuo* at 25 torr and ambient temperature for seven days and then weighed. The average yield for 8 syntheses was 35.85g (81.7% of theoretical). Its melting point was 151.5-152.0 °C.

Five grams of this crude product were dissolved in 50.00g of 1,4-dioxane. This solution was passed through 10 ml of silica gel/1,4-dioxane slurry in an addition funnel and directly charged into a 50 cm silica gel/1,4-dioxane chromatography column 1.5 cm in diameter with a holdup volume of 39.0 ml. The purified monomer was eluted in the fractions between 70 ml to 240 ml. This fraction was collected in a clean 500 ml round-bottom flask. The dioxane was then flash-evaporated at 40 torr and 45°C (113°F), and the monomer was dried for seven days at ambient temperature and 25 torr. The average yield for twenty

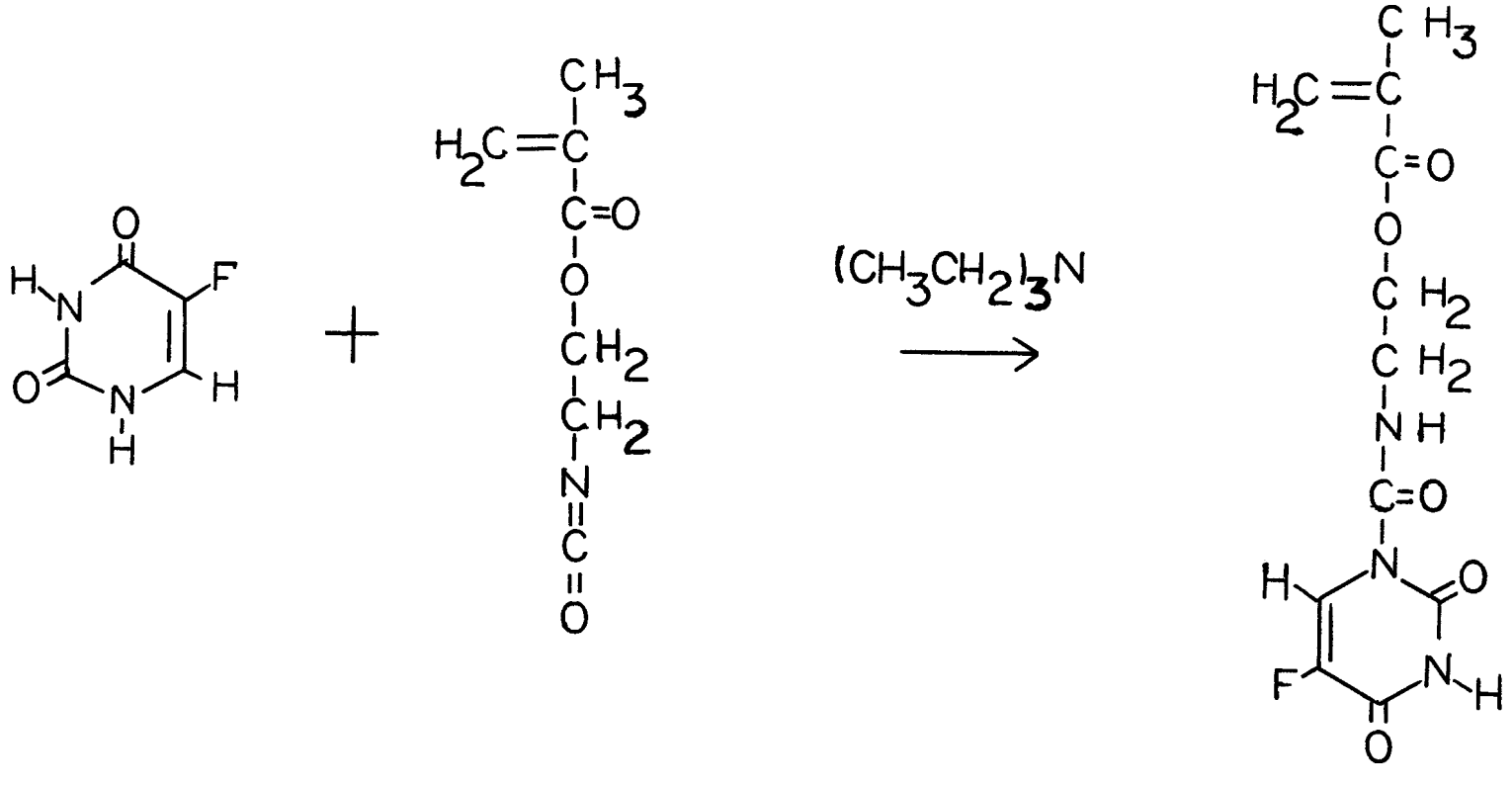


Figure Reaction of 5-fluorouracil with isocyanatoethylmethacrylate.

purification runs was 4.75 g.(94.9% of theoretical, 77.5% overall theoretical) of the purified, white, crystalline product. It had a sharp melting point of 154°Cd. Its infrared spectrum can be found in Figure 6.

This confirms the synthesis of the desired product. Figure 7 shows the IR spectrum of 5-FU. The melting point of 5-FU is 286°Cd.

The TLC R_f value for the purified monomer was found to be 0.809 using 1,4-dioxane and 0.158 using chloroform. No movement was observed with methanol(1% glacial acetic acid), ethyl ether (1% glacial acetate acid), benzene (1% glacial acetic acid), or hexane (1% glacial acetic acid). Using a mixture of 2%:98% by volume of 1,4-dioxane:chloroform mixture as the developer gave an R_f value of 0.560. The R_f value for a 98%:2% by volume of 1,4-dioxane:chloroform mixture as the developer was 0.980. Iodine was used to visualize the monomer.

At room temperature the monomer was found to be soluble in 1,4-dioxane, acetone, methylene chloride, chloroform, dimethyl sulfoxide, and cellosolve acetate. It was insoluble in n-butyl alcohol, carbon tetrachloride, toluene, n-heptane, ethyl ether, methyl isobutyl ketone, and benzene. Swelling occurred in n-butyl acetate, ethyl acetate, acetonitrile, methyl cellosolve, methyl ethyl ketone, γ-butyrolactone, and tetrahydrofuran. When heated to 80°C, the following solvents dissolved the monomer: n-butyl alcohol, n-butyl acetate, ethyl acetate, toluene, acetonitrile, methyl ethyl ketone, methyl isobutyl ketone, and γ-butyrolactone.

It is interesting to note that the monomer is thermally unstable. After being subjected to a 135.5°C oven for one-half hour and a 137.0°C oven for one-half hour, its melting point increased to

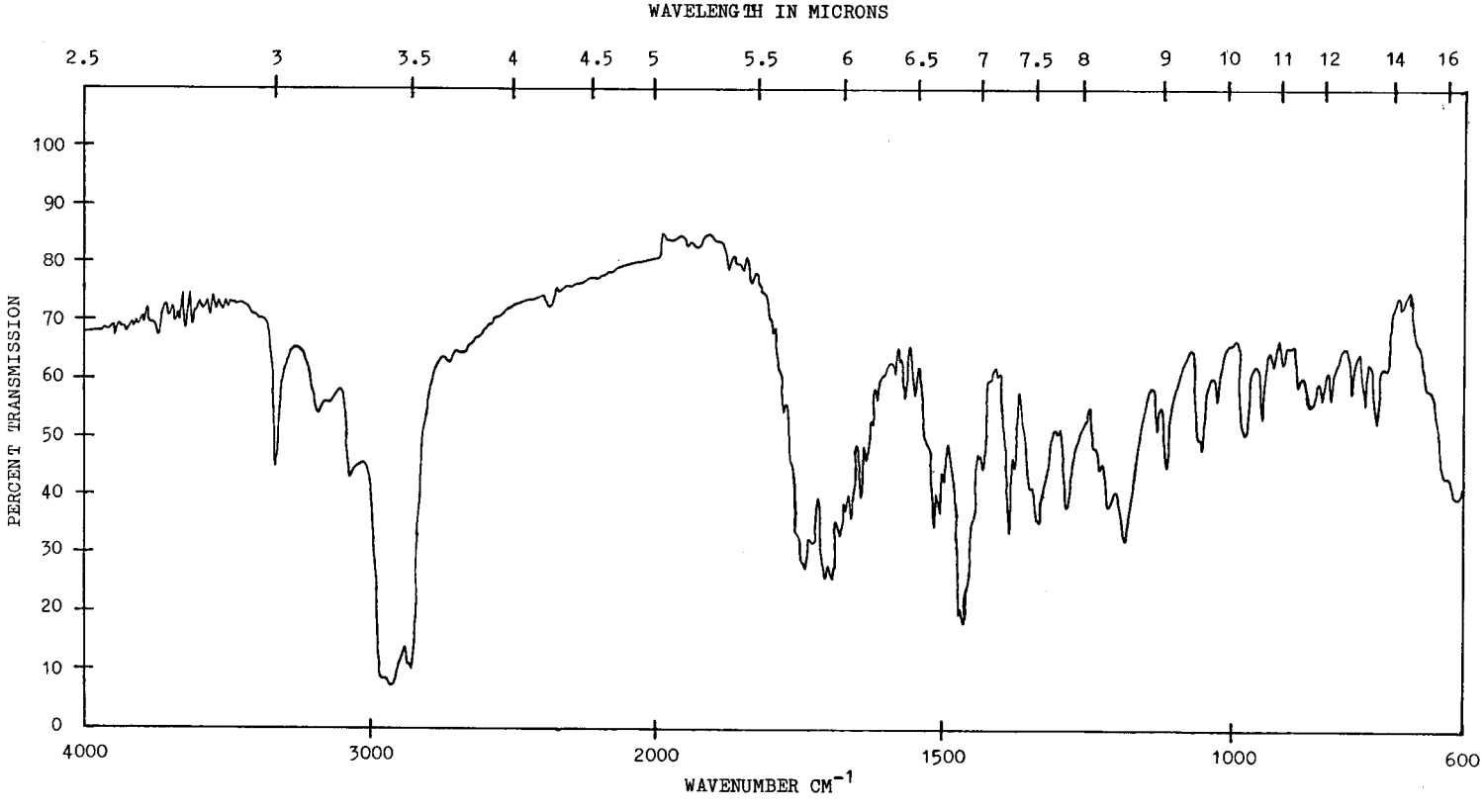


Figure 6- IR spectrum of EMCF

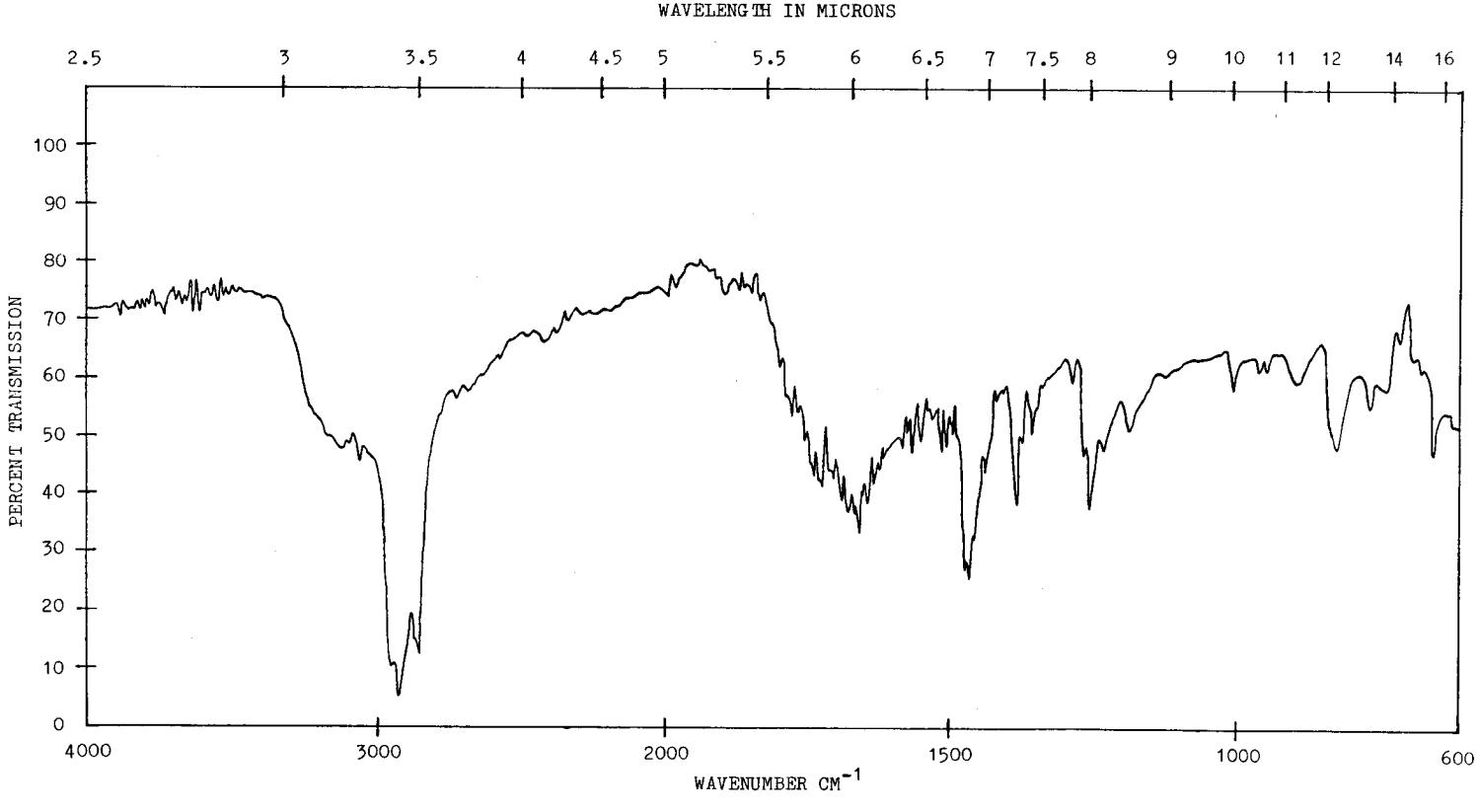


Figure 7- IR spectrum of 5-FU.

259°Cd. It also turned from white to brown. Another property of importance is its sensitivity to light when subjected to silica gel in an unprotected column. When elution from such a column was unsuccessful, the column was wrapped in aluminum foil and the successful results were obtained.

Preparation of 1-(N-2-ethylmethacrylacarbamoyl)uracil

To a 500 ml Erlenmeyer flask wrapped with aluminum foil, fitted with a calcium sulphate drying tube and magnetic stirring bar, were placed 5.00g (0.0446 moles) uracil, 7.00g (0.0451 moles) isocyanatoethyl methacrylate, 0.12 ml triethylamine, and 109g or 1,4-dioxiane. After allowing the reaction to proceed for five days while the flask was suspended over a stirring plate and stirring, the solution was filtered through a Whatman No. 4 filter paper into a 250 ml round-bottom flask. The dioxane was then flash-evaporated at 40 torr and 45°C (113°F) and the fluffy, white, crystalline product dried for seven days at ambient temperature and 25 torr. The yield was 6.58g (55.1% theoretical). Its melting point was sharp at 286.0°C.

Infrared analysis confirmed the synthesis of the desired product. Examination of the IR spectrum of the residue from filtration revealed it to be unreacted uracil. The IR spectrum of the residue from filtration revealed it to be unreacted uracil. The IR spectrum of uracil is given in Figure 8. The melting point of uracil is 335°Cd. The IR spectrum of the product is shown in Figure 9.

The monomer was found to be soluble in acetone, 1,4-dioxane, methylene chloride, chloroform, and acetonitrile. It was insoluble in benzene, γ-butyrolactone, THF, cellosolve acetate, butyl alcohol,

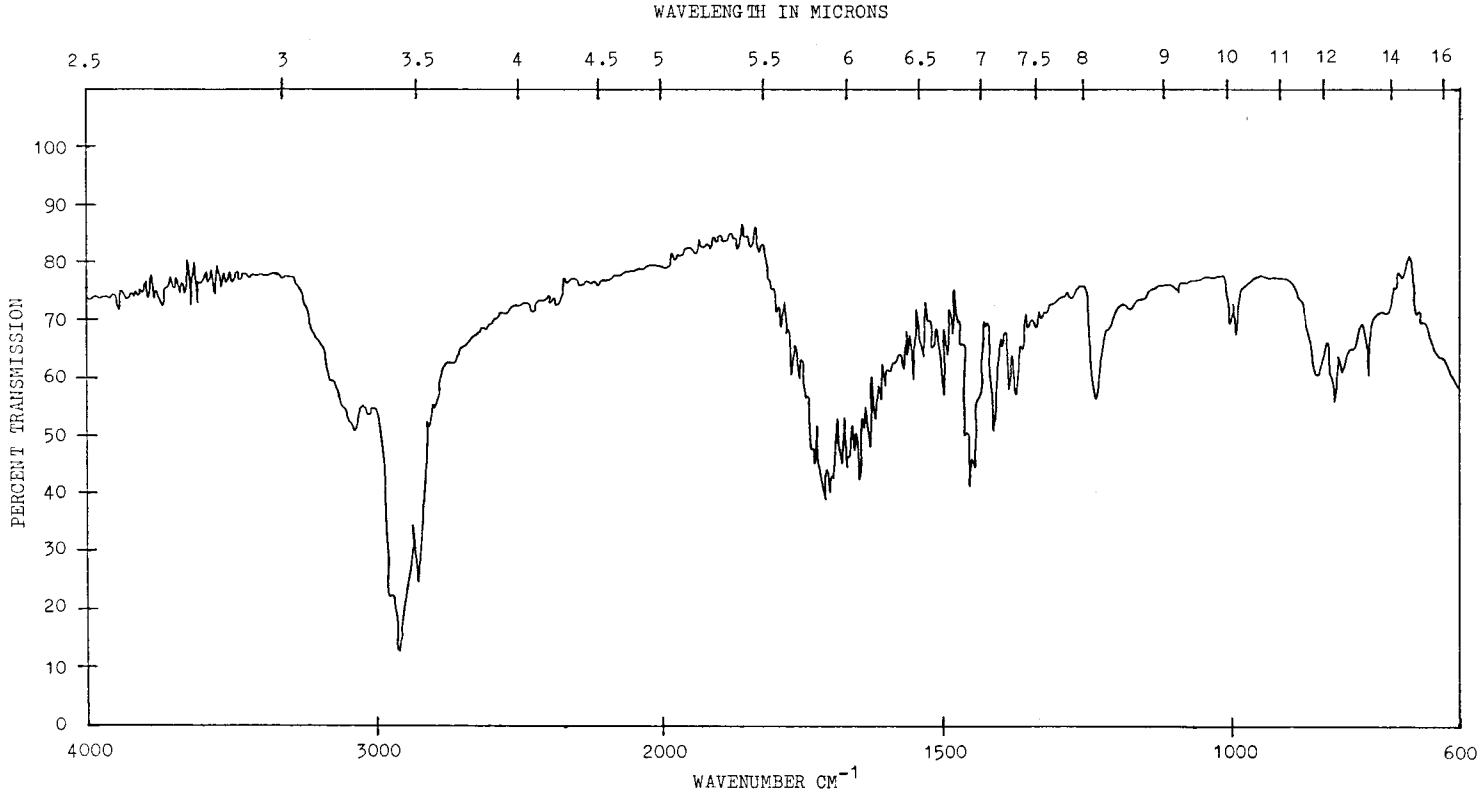


Figure 8- IR spectrum of uracil.

butyl acetate, ethyl acetate, carbon tetrachloride, toluene, n-heptane, ethyl ether, methyl cellosolve, MEK, and MIBK. It swells in DMSO.

Preparation of 1-(N-2-ethylmethacrylcarbamoyl)piperidine

In a 500 ml Erlenmeyer flask wrapped in aluminum foil, fitted with a calcium sulphate drying tube and magnetic stirring bar, were placed 5.00g (0.0575 moles) piperidine(98%), 143g 1,4-dioxane, 0.16 ml triethylamine, and 9.5 g isocyanatoethylmethacrylate. After allowing the reaction to proceed for 5 days while suspended over a stirring plate and stirring, the solution was filtered through a Whatman No. 4 filter paper into a 500 ml round-bottom flask. The dioxane was flash-evaporated at 40 torr and 45°C (113°F) and the off-white, crystalline product was dried 7 days at ambient temperature and 25 torr. The yield was 13.82g (0.0575 moles, 100% theoretical). The melting point of the monomer was 83.5-84.0 °C. Infrared analysis confirmed synthesis of the desired product. The spectrum can be found in Figure 10.

The monomer was found to be soluble in acetone, methylene chloride, chloroform, carbon tetrachloride, MEK, MIBK, THF, DMSO, 1,4-dioxane, butyl alcohol, butyl acetate, ethyl acetate, toluene, benzene, methyl cellosolve, cellosolve acetate, and γ-butyrolactone. It was insoluble in n-heptane, ethyl ether, and acetonitrile.

Preparation of Poly[1-(N-2-ethylmethacrylcarbamoyl)-5-fluorouracil]

In a 500 ml Erlenmeyer flask wrapped with aluminum foil was added 10.0000g (0.0351 moles) 1-(N-2-ethylmethacrylcarbamoyl)-5-fluorouracil (EMCF), 100g 1,4-dioxane, and a stirring bar. The flask was

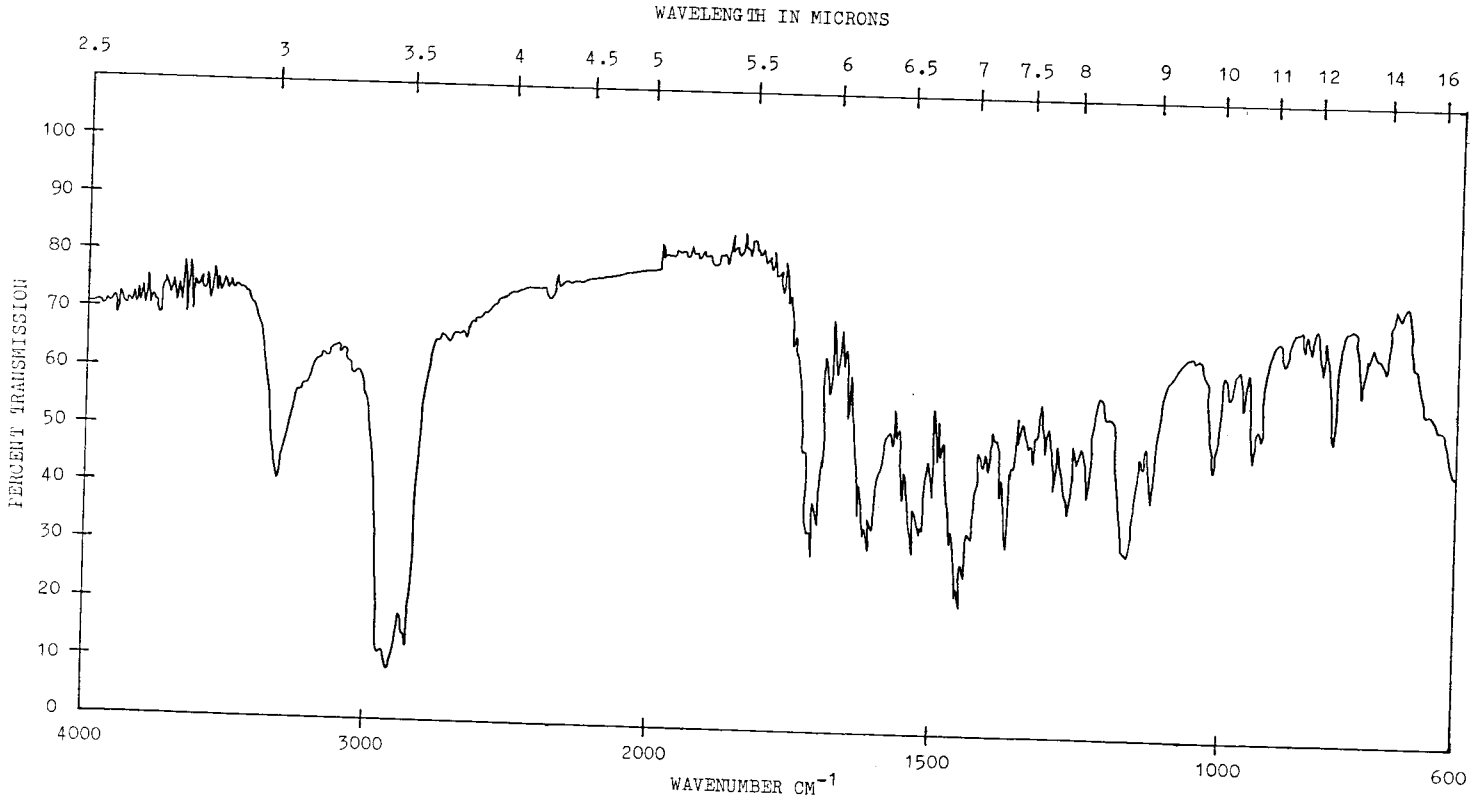


Figure 10-- IR spectrum of 1-(N-2-ethylmethacrylcarbamoyl)piperidine

sparged with dry N_2 for one hour. At the end of this time, 0.0576g (0.000351 moles) AIBN was added to the flask, a drying tube containing indicating Drierite, and also flushed with dry N_2, was fitted on top, and the flask was placed into a 75.0-80.0°C oil bath for twenty hours. The polymer had precipitated from solution. After washing the polymer in methanol by pouring the mixture of insoluble polymer and 1,4-dioxane into 200 ml of anhydrous methanol and filtering onto a sintered glass funnel, the polymer was placed in a vacuum oven in an evaporating dish for seven days at ambient temperature and 15 torr. The dried product weighed 9.39273 (93.9% theoretical).

The IR spectrum (Figure 11) showed an absence of peaks at 940 cm^{-1} and 970 cm^{-1}, indicating polymerization through the vinyl group, and also the retention of peaks due to the fluorouracil group, most notably the peak at 1260 cm^{-1}, indicated synthesis of the desired product.

The polymer was off-white in color, and found to be insoluble in toluene, n-heptane, acetonitrile, ethyl ether, methyl cellosolve, MEK, MIBK, acetone, 1,4-dioxane, n-butyl alcohol, n-butyl acetate, ethyl acetate, methylene chloride, chloroform, carbon tetrachloride, γ-butyrolactone, DMSO, benzene, cellosolve acetate, THF, pyridine, carbon disulfide, N,N-dimethyl acetamide, N,N-dimethyl formamide, 1.5N HCl, water, isopropanaol, hexafluorobenzene, n-propanol, ethanol, cyclohexanol, cyclohexane, xylene, glycerine, chlorobenzene, trichloroethane, and 1,2-dichloroethane. However, the product did swell in: 1,4-dioxane, DMSO, γ-butyrolactone, chlorobenzene, cyclohexanol, glycerine, propionaldehyde, pyridine, N,N-dimethyl acetamide, and

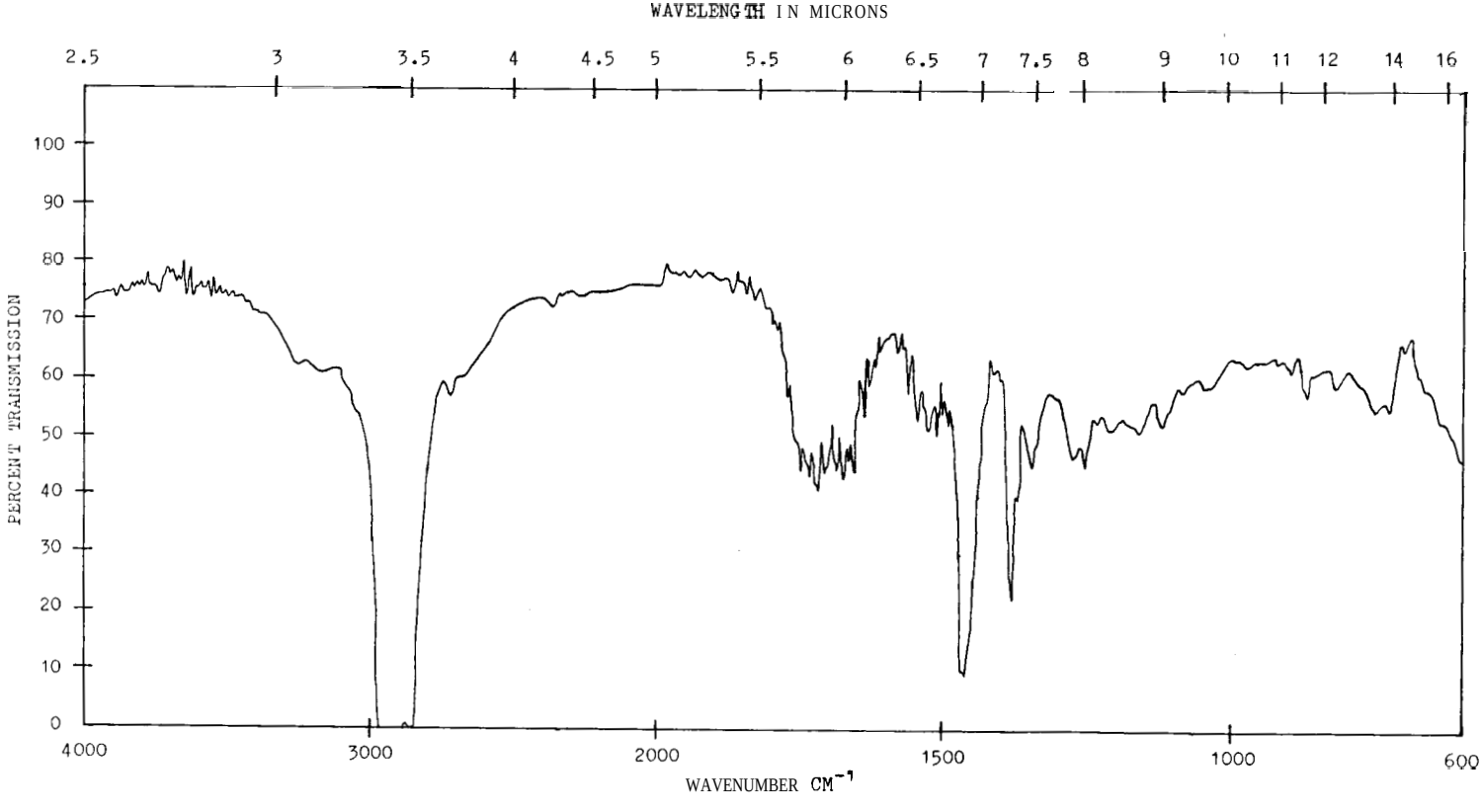


Figure 11- IR spectrum of poly[EMCF].

and N,N-dimethyl formamide. A solution of 5% NaOH did dissolve the product, but with decomposition. It did not melt, but started to decompose at 278°C.

Preparation of Poly[1-(N-2-ethylmethacrylcarbamoyl)uracil]

To a 500 ml Erlenmeyer flask fitted with a calcium sulfate drying tube and magnetc stirring bar was added 5.0000g (0.0187 moles) of 1-(N-2-ethylmethacrylcarbamoyl)uracil and 50.00g of 1,4-dioxane. After sparging for 1 hour with dry N_2, 0.0299g (0.000182 moles) of AIBN was added to the flask which was then submerged in an oil bath at 75-80°C for 20 hours while stirring. At the end of the reaction period, the insoluble polymer was filtered onto a sintered glass funnel, washed with methanol, and then vacuum oven at 25 torr at ambient temperature for 7 days in an evaporating dish. The yield was 4.5804g (91.6% of theoretical) of very fluffy, white polymer.

Infrared analysis confirmed synthesis of the desired product. The IR spectrum is shown in Figure 12. It started to decompose at 278°C.

The polymer was not soluble in any of the solvents tried. It swells in chloroform (on which it floats), carbon tetrachloride (on which it floats), acetonitrile, γ-butyrolactone, DMSO, and benzene. It is insoluble in acetone, dioxane, butyl alcohol, butyl acetate, ethyl acetate, methylene chloride, toluene, n-heptane, ethyl ether, methyl cellosolve, cellosolve acetate, THF, MEK, and MIBK.

Prepareation of Poly[1-(N-2-ethylmethacrylcarbamoyl)piperidine]

To a 500 ml Erlenmeyer flask fitted with calcium sulfate drying tube and a magnetic stirring bar was added 5.0000g (0.0208

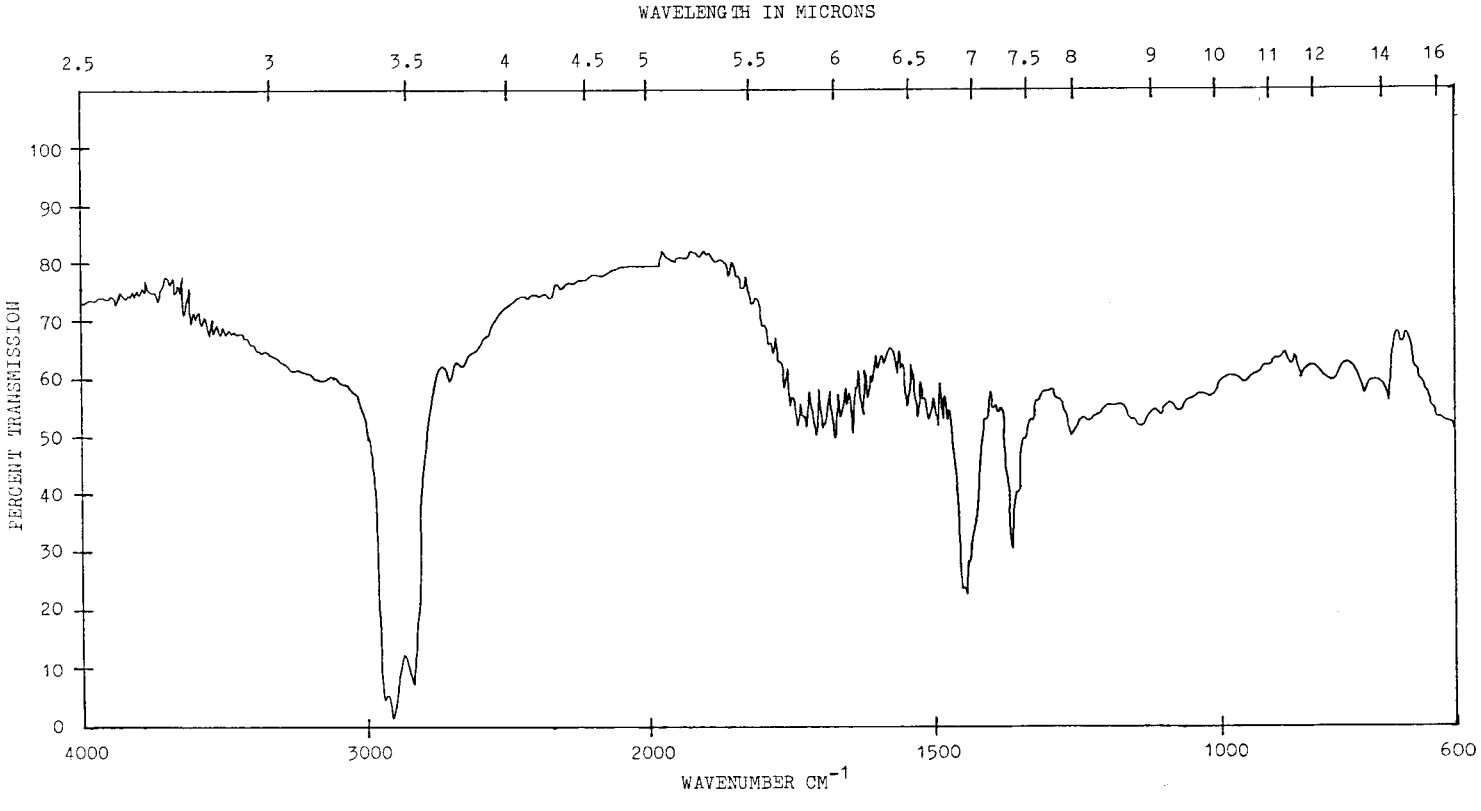


Figure 12- IR spectrum of poly[1-(N-2-ethylmethacrylcarbamoyl)uracil].

moles) of 1-(N-2-ethylmethacrylcarbamoyl)piperidine and 50.00g of 1,4-dioxane. After sparging for 1 hour with dry N_2, 0.0333g (0.000203 moles) of AIBN was added to the flask which was then submerged in an oil bath at 75-80°C for 20 hours while stirring. At the end of the reaction period, the insoluble polymer was filtered onto a sintered glass funnel, washed with methanol, and then vaccum dried at 25 torr and ambient temperature for 7 days in an evaporating dish. The yield was 1.4941g (29.9% of theoretical) of yellow, crystalline, hard, brittle polymer.

Infrared analysis confirmed the synthesis of the desired product, and its spectrum can be found in Figure 13. It did not melt, but started decomposing at 168°C.

The polymer was found not to be soluble in any of the solvents tried. It was insoluble in acetone, acetonitrile, and ethy acetate. It swelled in 1,4-dioxane, butyl alcohol, butyl acetate, methylene chloride (on which it floats), chloroform (on which it floats), carbon tetrachloride (on which if floats), toluene, n-heptane, ethyl ether, methyl cellosolve, MEK, MIBK, cellosolve acetate, THF, γ-butyrolactone, DMSO, and benzene.

Preparation of Homopolymers and Copolymers of Methyl Acrylate, Butyl Acrylate, Methyl Methacrylate, Butyl Methacrylate, Stearoyl Methacrylate, and Hydroxyethyl Methacrylate

To a 500 ml Erlenmeyer flask fitted with a calcium sulfate drying tube and magnetic stirring bar was added the appropriate amounts of comonomer and EMCF along with 100.00g of 1,4-dioxane. After the flask was sparged for 1 hour with dry N_2 the appropriate amount

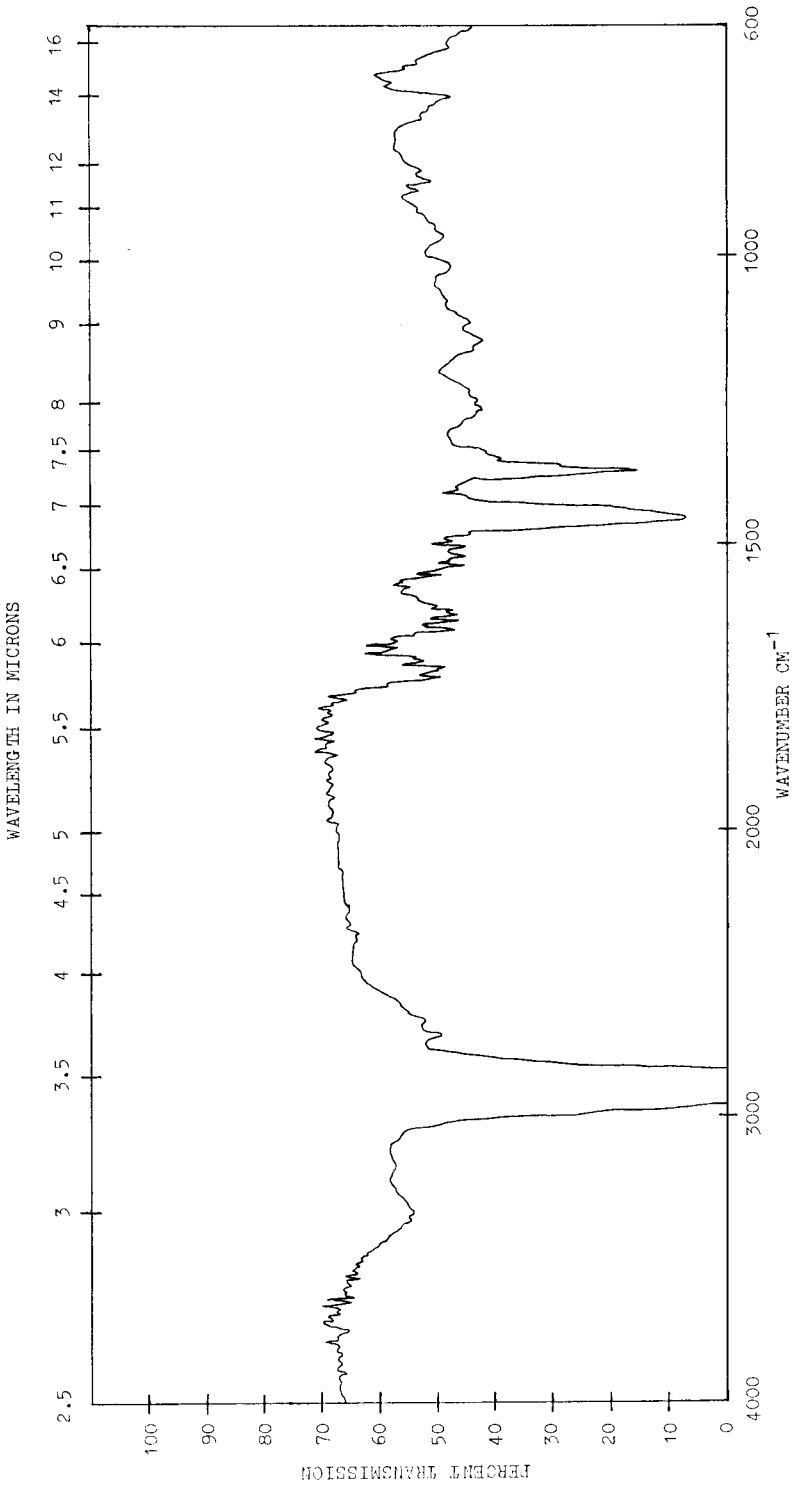


Figure 13- IR spectrum of poly[1-(N-2-ethylmethacrylcarbamoyl)piperidine].

of AIBN was added (see Tables 8 and 9). The flask was then submerged in a 75-80°C oil bath for twenty hours while the solution was stirred. At the end of the reaction period, the reaction mixture was poured into 200 ml of methanol, collected on a sintered glass funnel, and then washed three times with methanol. In the case of the homopolymers, the methanol was cooled to -20°C to insure complete precipitation. The polymer or copolymer was then transferred to an evaporating dish and placed in a vacuum oven at 25 torr and ambient temperature for 7 days. The yields and melting points for the various products are shown in Table 9.

Infrared anaylsis confirmed the presence of the monomers charged into the reaction flask, with the magnitude of the peaks due to each monomer varying according to the amount present in the copolymers. The spectra of the homopolymers can be found in Figures 14-19. Representative spectra from each group of copolymers can be found in Figures 20-25.

Solubilities of each of the homopolymers and copolymers in various solvents can be found in Tables 10-13.

Elemental Analysis

Elemental analysis was performed on EMCF, poly(EMCF), all the methyl and butyl acrylate copolymers, 50% MMA, 50% BMA, 50% StMA, and 50% HEMA. The values obtained for EMCF agreed well with its assigned structure. For poly(EMCF) and the copolymers, however, the values did not agree well. A recalculation was made based on the assumptions that

TABLE *8*

SYNTHESIS DATA

Comonomer Charge	Amount of Comonomer (g)	Amount of Comonomer (moles)	Amount of EMCF (g)	Amount of EMCF (moles)
100% MA	10.0050	0.116	0	0
25% MA	0.9160	0.0106	9.0859	0.0318
50% MA	2.3185	0.0269	7.6727	0.0269
75% MA	4.7519	0.0552	5.2489	0.0184
100% BA	10.0050	0.0781	0	0
25% BA	1.3037	0.0102	8.6990	0.0305
50% BA	3.1012	0.0242	6.9008	0.0242
75% BA	5.7422	0.0448	4.2952	0.0149
100% MMA	10.0020	0.0999	0	0
25% MMA	1.0474	0.0105	8.9526	0.0314
50% MMA	2.5981	0.0260	7.4019	0.0260
75% MMA	5.1300	0.512	4.8726	0.0171
100% BMA	10.0010	0.0703	0	0
25% BMA	1.4239	0.0100	8.5761	0.0301
50% BMA	3.3282	0.0234	6.6752	0.0234
75% BMA	5.9949	0.0422	4.0075	0.0141
100% StMA	10.0017	0.0295	0	0
25% StMA	2.8344	0.0295	7.1650	0.0251
50% StMA	5.4283	0.0160	4.5736	0.0160
75% StMA	7.8085	0.0231	2.1925	0.0769
100% HEMA(96%)	10.4167	0.0768	0	0
25% HEMA(96%)	1.3755	0.0101	8.6800	0.0304
50% HEMA(96%)	3.264	0.0241	6.8669	0.0241
75% HEMA(96%)	6.0186	0.0444	4.2220	0.0148

TABLE 9

AIBN, YIELD, MELTING POINT, AND APPEARANCE

Comonomer Charge	Amount of AIBN, (g)	(molesX10^2)	Yield (g)	Melting Point (°C)	Appearance[a]
100% MA	0.1908	0.116	7.1839	86.0-87.0	s,g,cl,c
25% MA	0.0703	0.0429	9.3591	234d	ow,cr,h,b
50% MA	0.0883	0.0583	9.9618	238d	ow,cr,h,b
75% MA	0.1285	0.0783	8.9311	242d	ow,cr,h,b
100% BA	0.1282	0.0781	7.0007		f,t,cl,c
25% BA	0.0664	0.0405	9.5864	247d	w,cr,h,b
50% BA	0.0805	0.0490	8.8238	242d	ow,cr,h,b
75% BA	0.0981	0.0597	9.5864	238d	ow,cr,h,b
100% MMA	0.1640	0.0999	9.6655	147.0-148.0	w,cr,c,h
25% MMA	0.0695	0.0423	8.4539	257d	w,cr,h,b
50% MMA	0.0860	0.0524	9.8723	239d	ow,cr,h,b
75% MMA	0.1125	0.0685	9.9310	238d	ow,cr,h,b
100% BMA	0.1154	0.0703	9.2463	108.0-112.0	cl,c,h,a
25% BMA	0.0658	0.0401	6.8444	265d	w,cr,h,b
50% BMA	0.0770	0.0469	9.1100	254d	ow,cr,h,b
75% BMA	0.0928	0.0565	8.9687	238d	ow,cr,h,b
100% StMA	0.0486	0.0299	6.8475	35.0-35.5	w,s,wx
25% StMA	0.0554	0.0337	7.4972	264d	w,cr,h
50% StMA	0.0526	0.0320	9.1095	218d	ow,a,s,wx
75% StMA	0.0505	0.0308	9.6711	84.0-86.0	ow,a,s,wx
100% HEMA	0.1262	0.0769	9.9946	128d	cl,cr,c,h,b
25% HEMA	0.0666	0.0406	9.6960	255d	w,cr,h
50% HEMA	0.0798	0.0486	9.9076	244d	w,cr,h
75% HEMA	0.0972	0.0592	8.7843	230d	w,cr,h

[a] s=soft; g=gummy; cl=clear; c=colorless; ow=offwhite; cr=crystalline; h=hard; b=brittle; f=fluid; t=tacky; w=white; a=amorphous; and w=waxy.

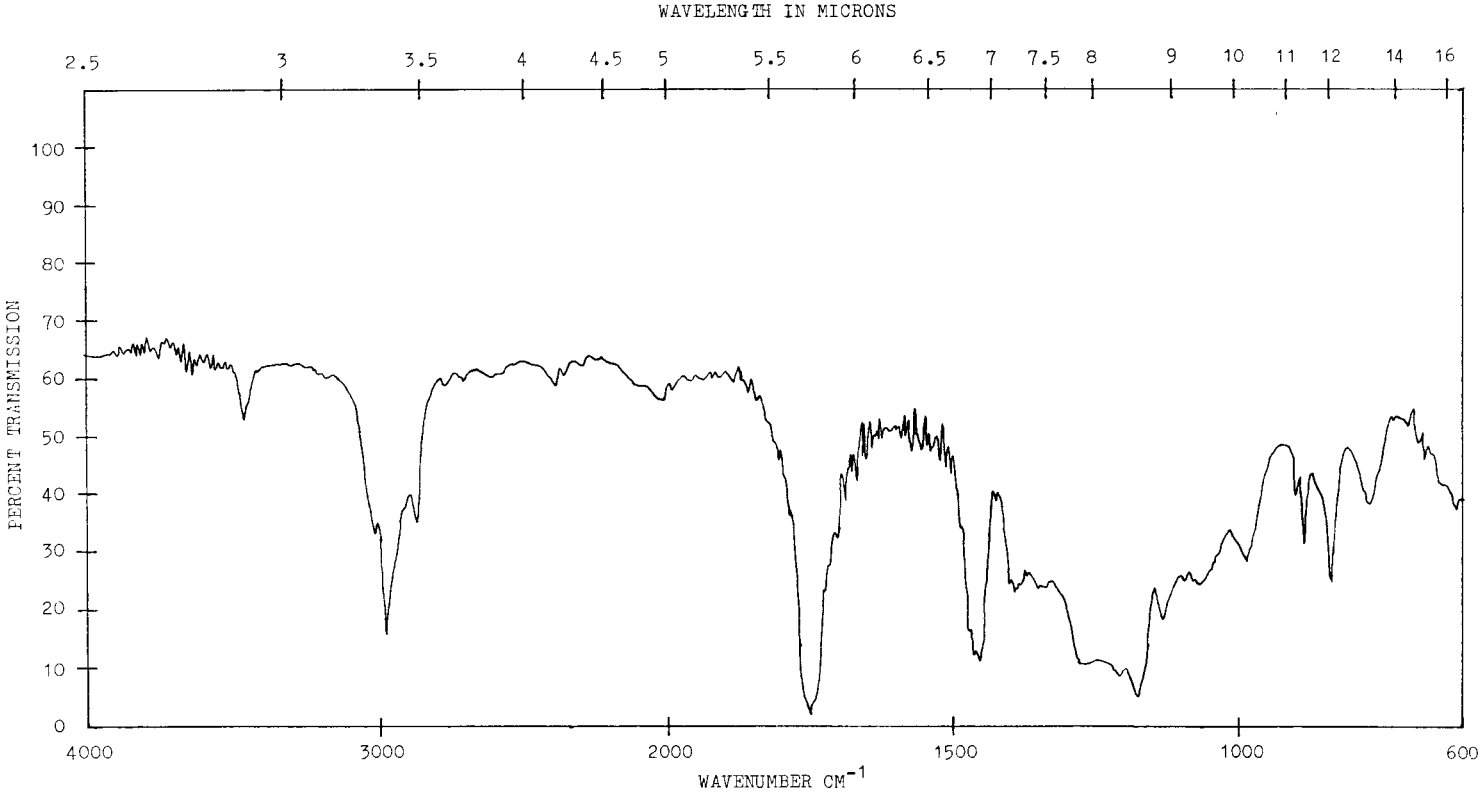


Figure 14- IR spectrum of poly[MA].

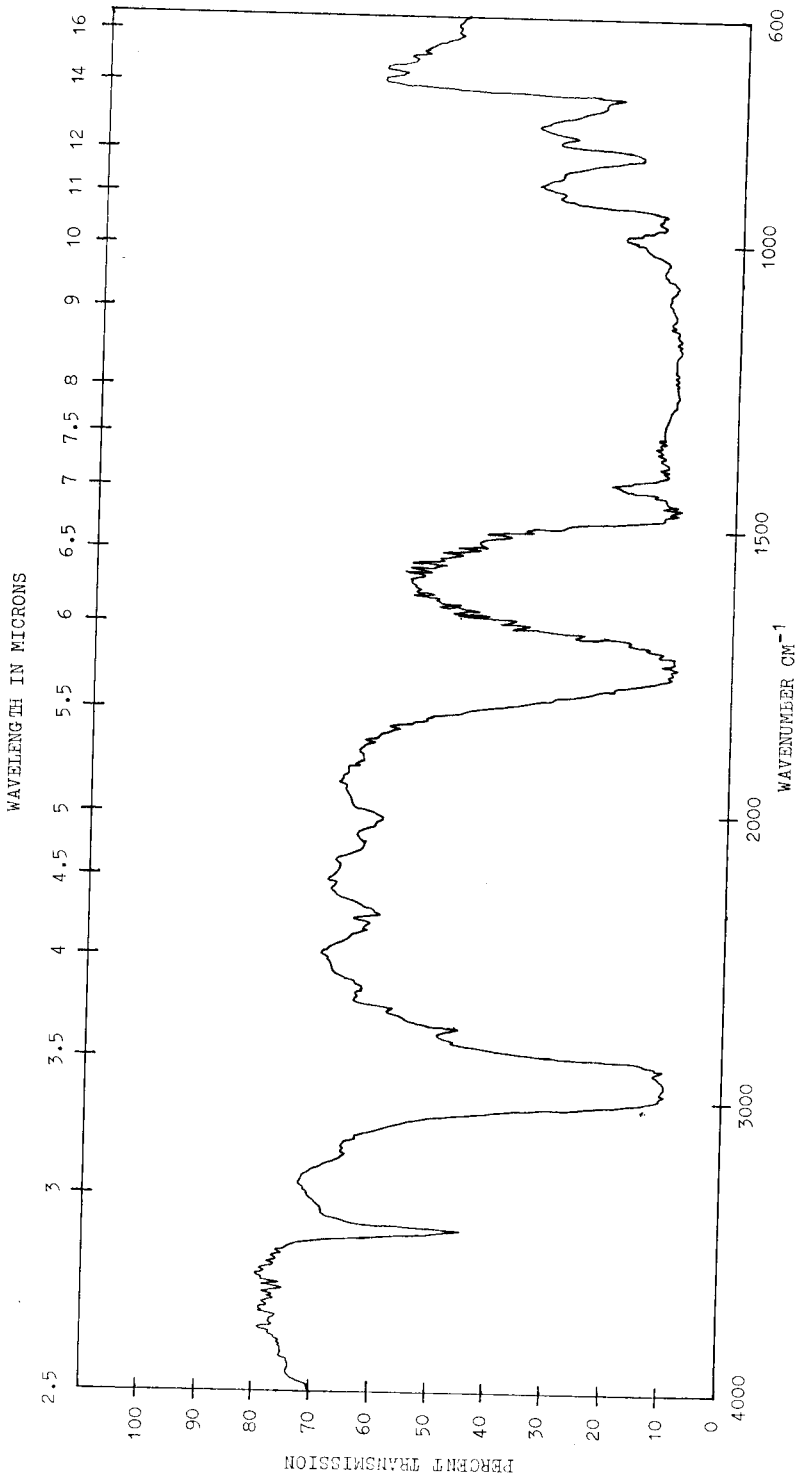


Figure 15- IR spectrum of poly[BA].

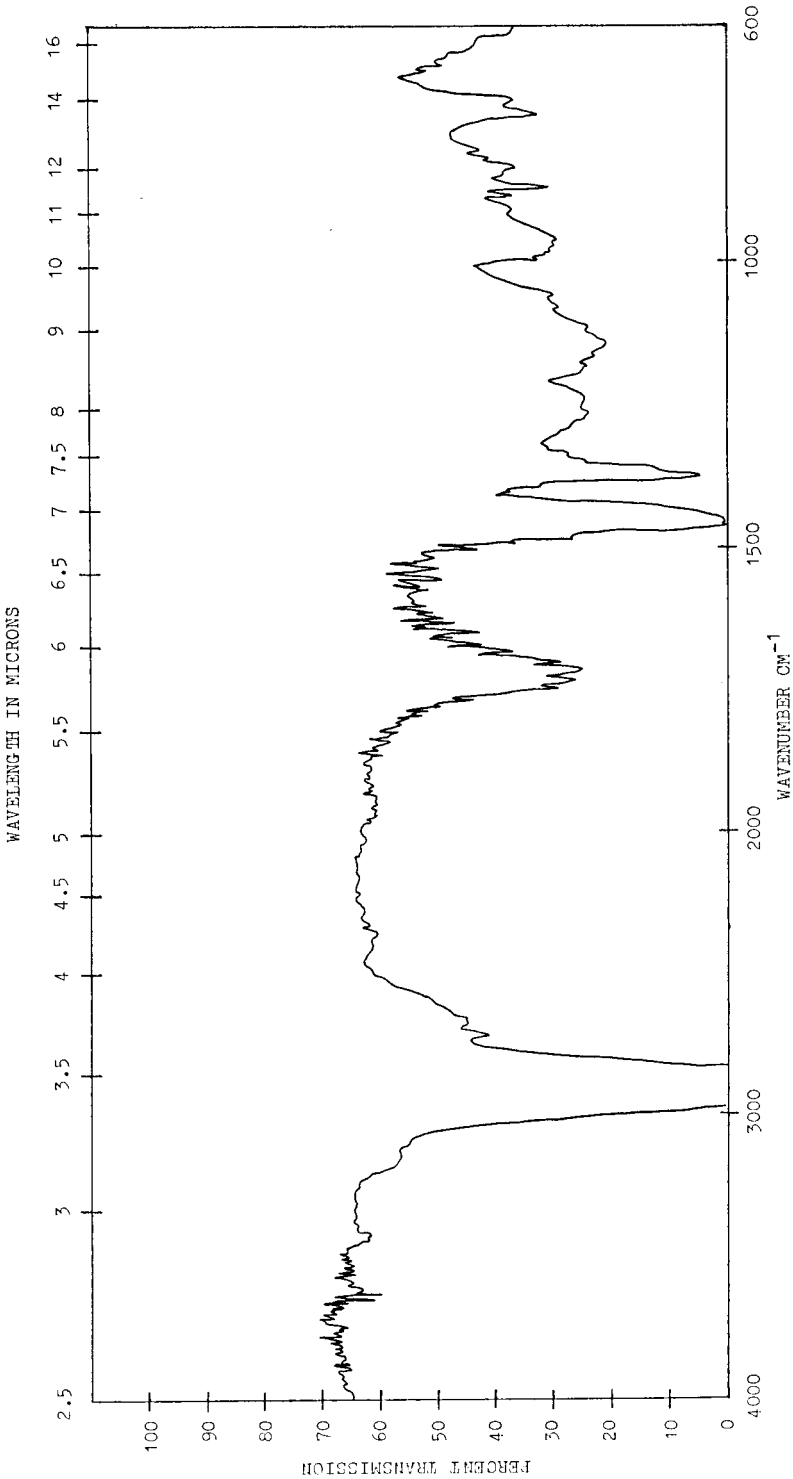


Figure 16- IR spectrum of poly[MMA]

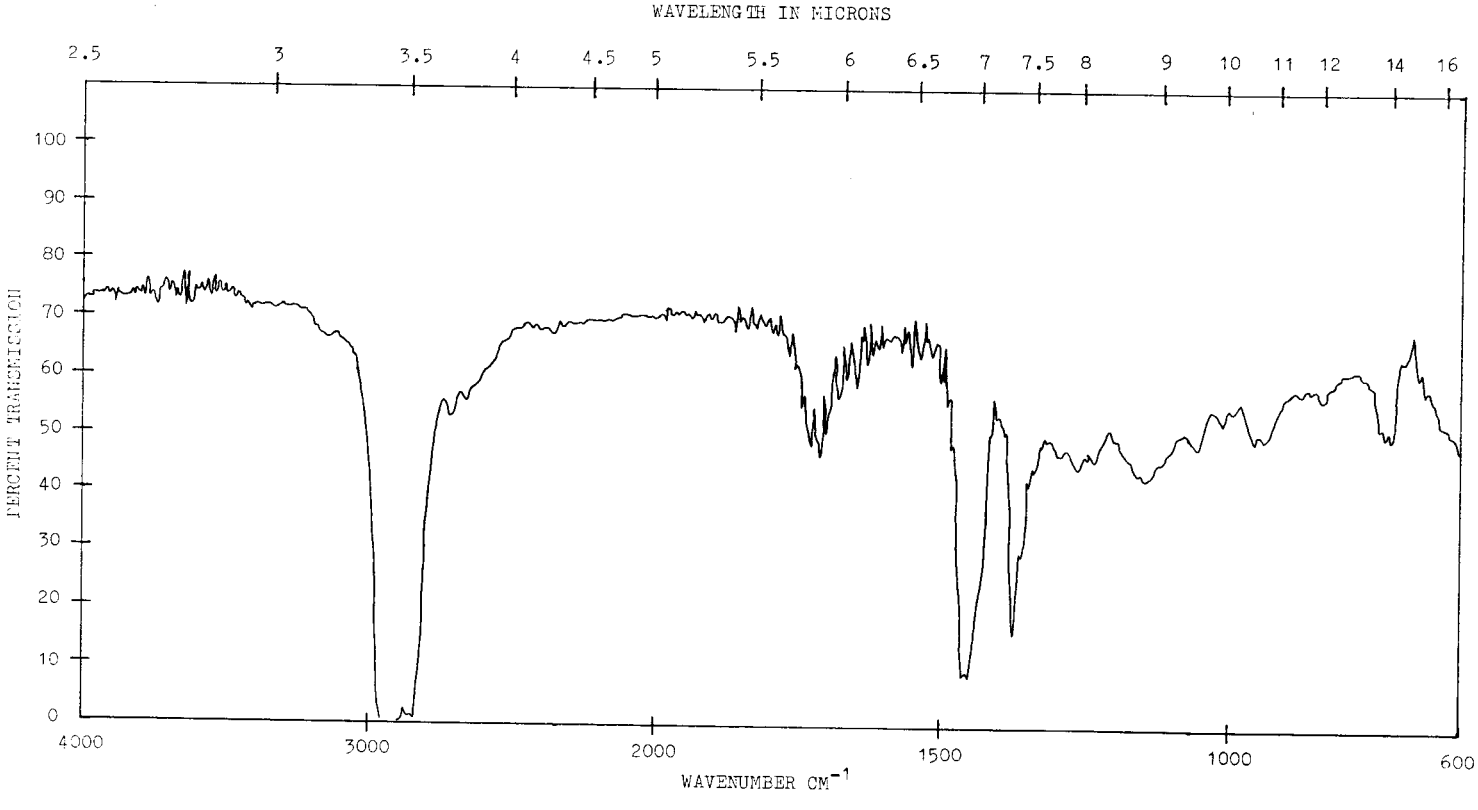


Figure 17- IR spectrum of poly[BMA].

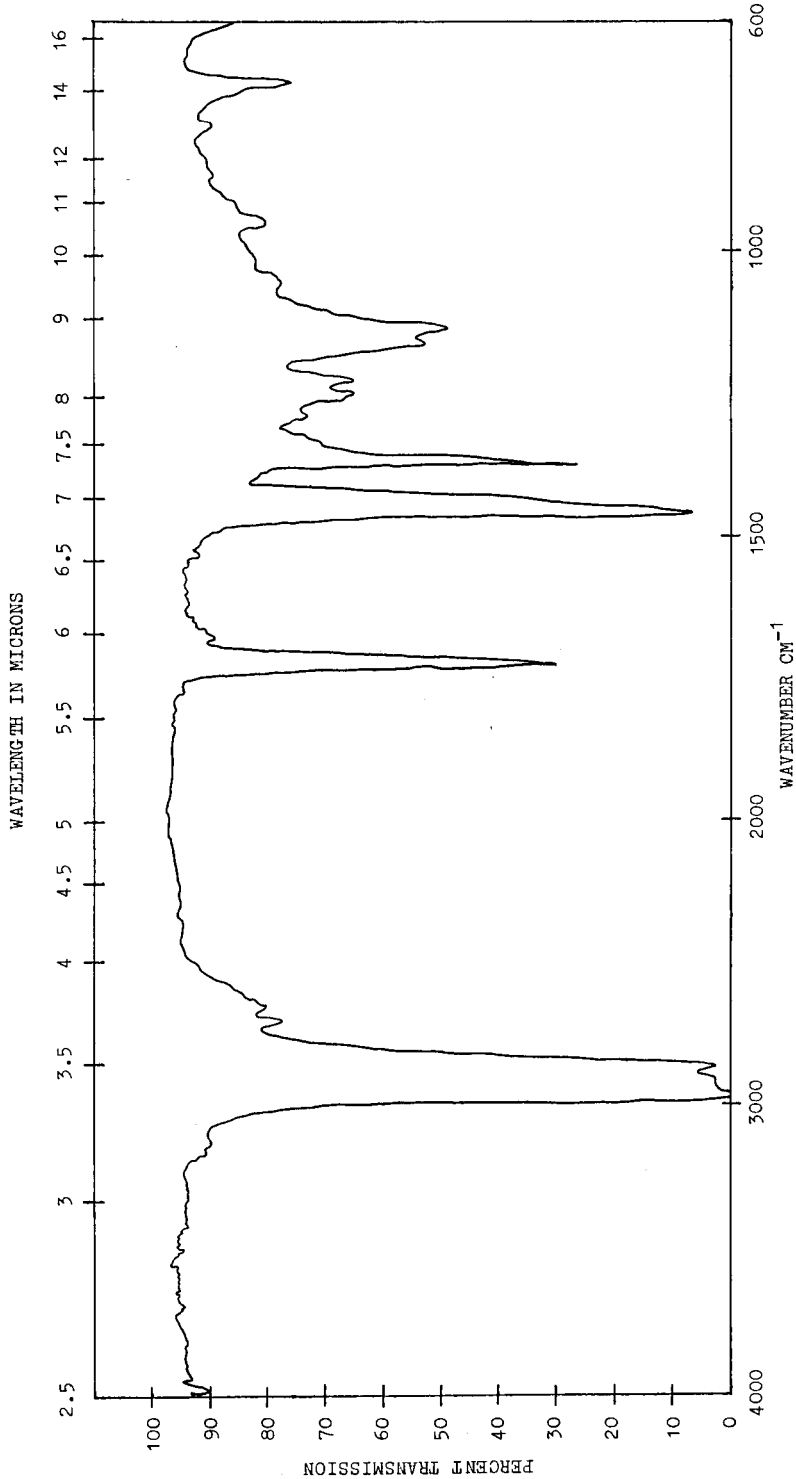


Figure 18- IR spectrum of poly[StMA]

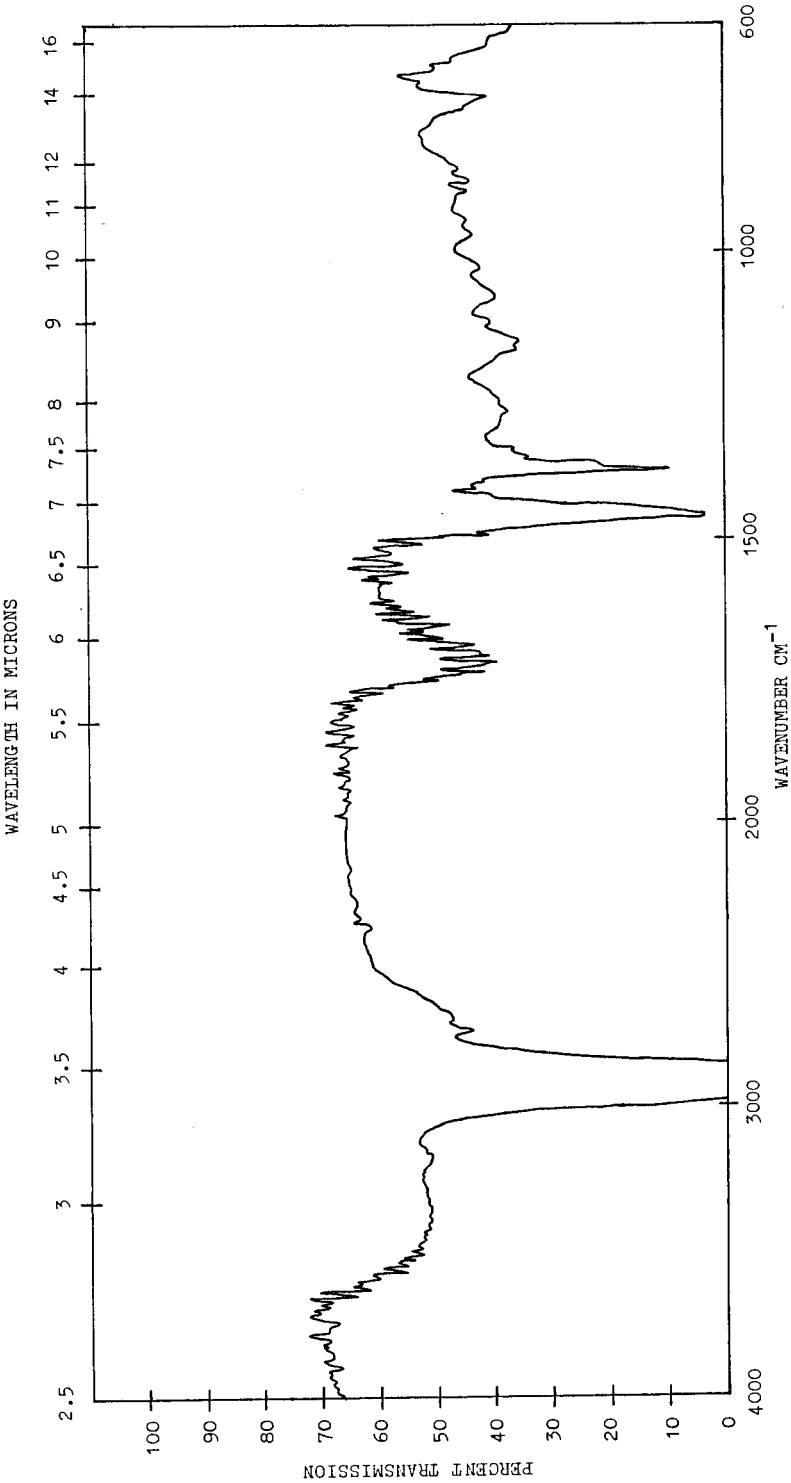


Figure 19- IR spectra of poly[HEMA].

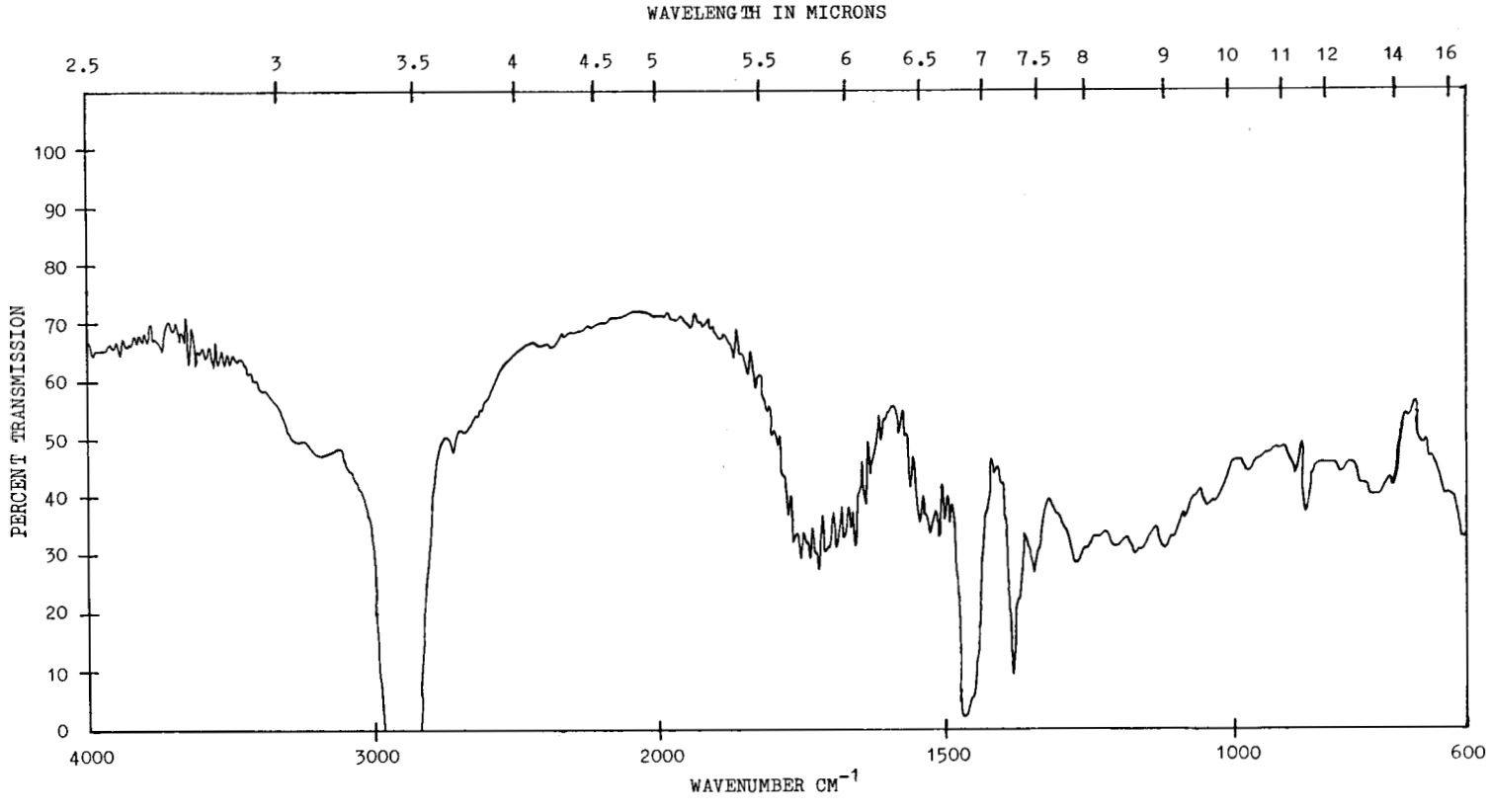


Figure 20- IR spectrum of copolymer charged as 50 mole% MA/50 mole% EMCF.

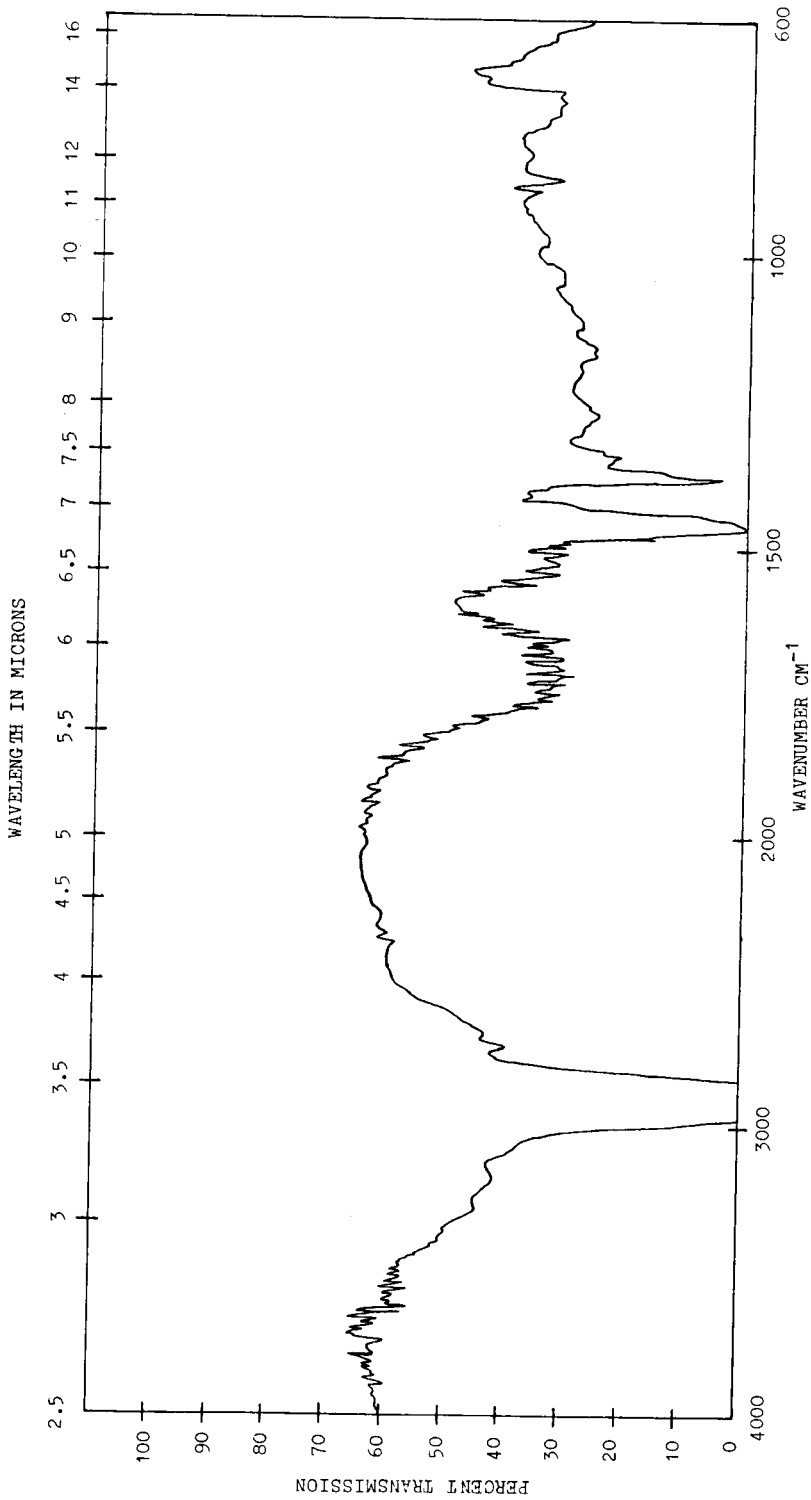


Figure 21- IR spectrum of copolymer charged as 25 mole% BA/75 mole% EMCF.

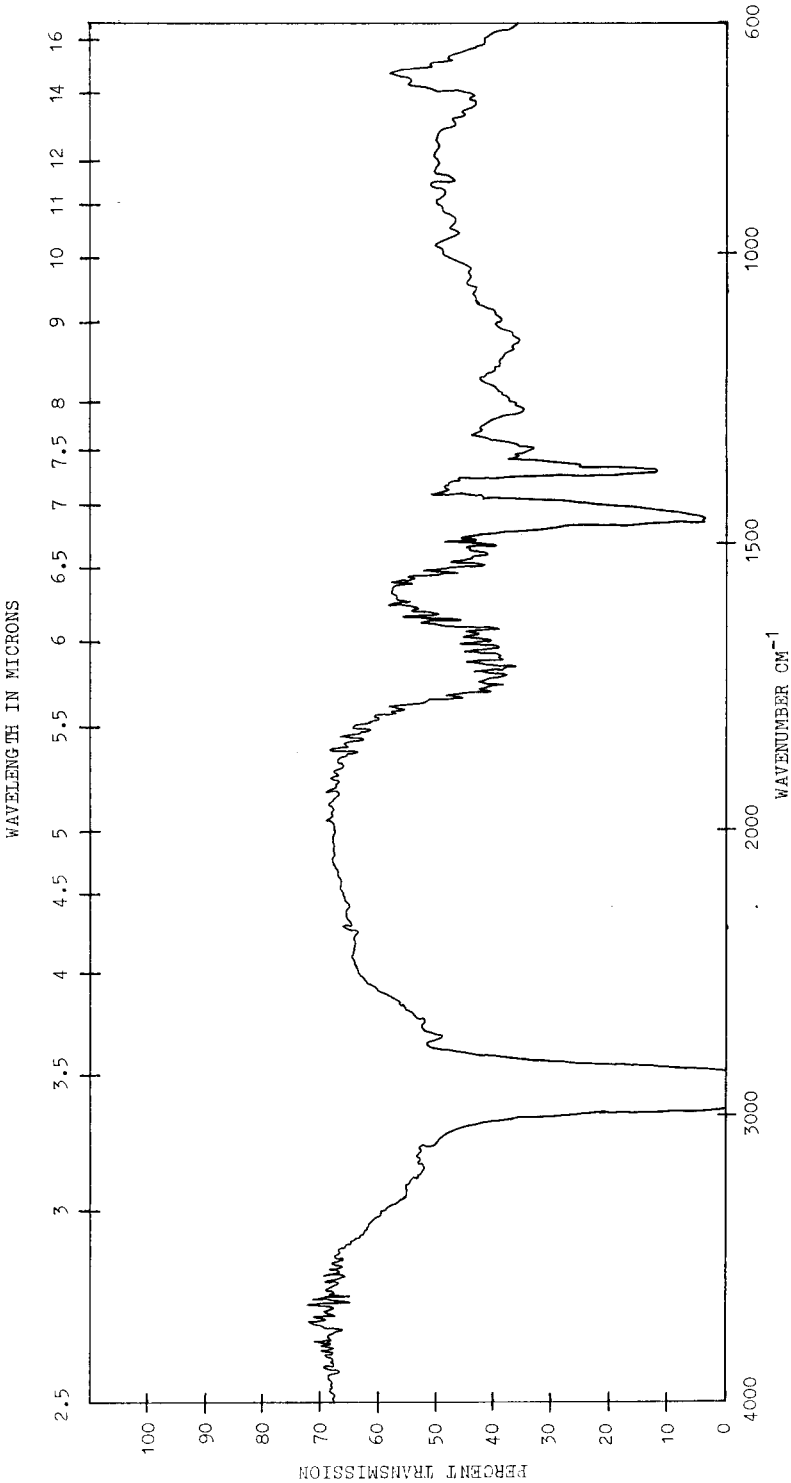


Figure 23- IR spectrum of copolymer charged as 50 mole% BMA/50 mole% EMCF

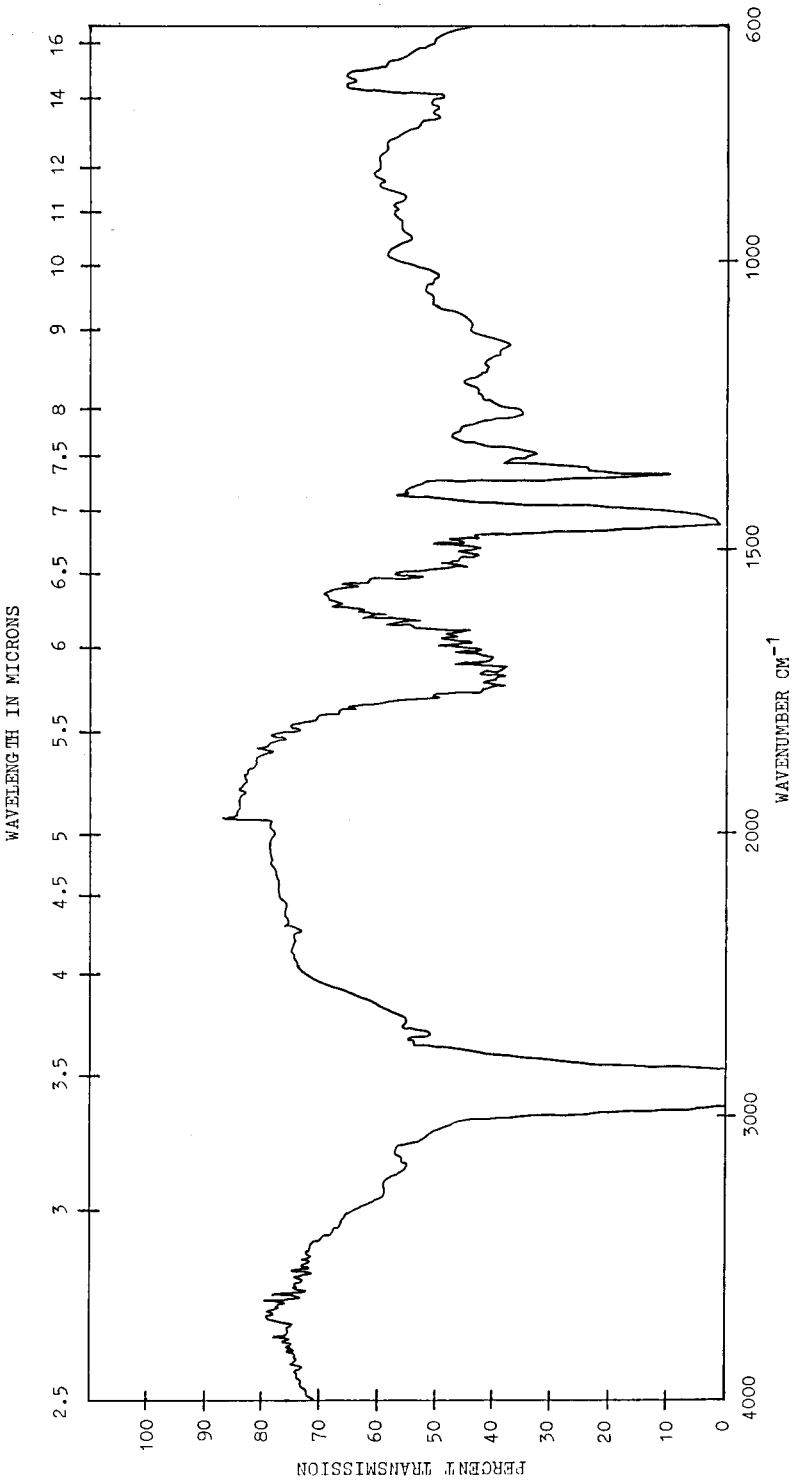


Figure 24- IR spectrum of copolymer charged as 25 mole% StMA/75 mole% EMCF

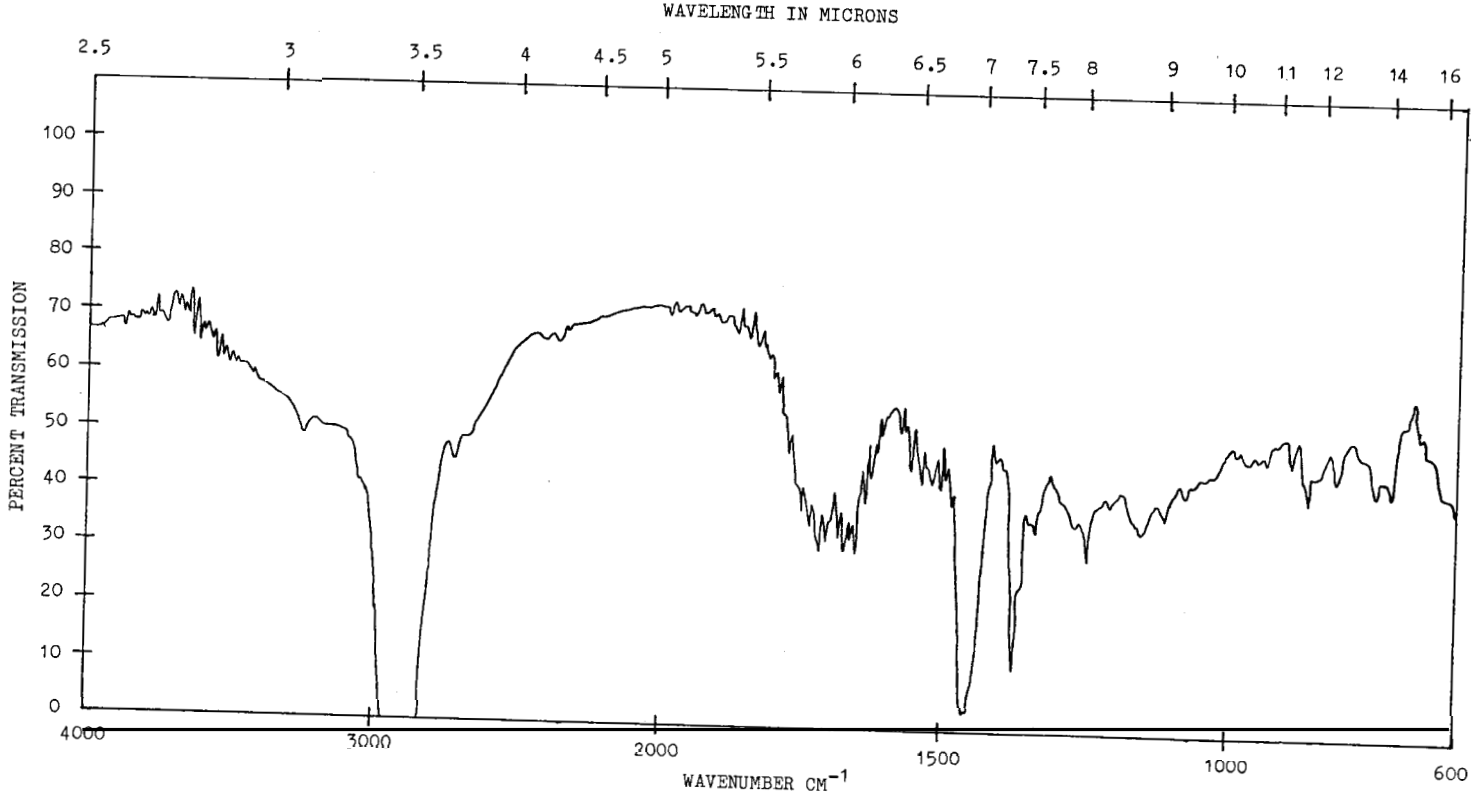


Figure 25- IR spectrum of copolymer charged as 50 mole% HEMA/50 mole% EMCF.

TABLE 10

SOLUBILITIES OF HOMOPOLYERS[a]

Solvent	MA	BA	MMA	BMA	StMA	HEMA
Acetone	s	s	s	s	sw	i
Acetonitrile	s	sw	s	i	sw	i
Benzene	s	s	s	s	sw	s
Butyl acetate	s	s	s	s	i	s
Butyl alcohol	i	s	i	s	sw	s
γ-Butylrolactone	s	sw	s	i	s	i,f
Carbon tetrachloride	s	s	s	s	sw,f	s
Cellosolve acetate	s	s	s	s	sw	s
Chloroform	s	s	s	s	sw,f	s
1,4-Dioxane	s	s	s	s	sw	s
DMSO	s	sw	s	sw	s	i,f
Ethyl acetate	s	s	s	s	sw	s
Ethyl ether	i	s	sw	s	sw	sw
n-Heptane	sw	s	s	s	i	s
MEK	s	s	s	s	sw	s
Methyl cellosolve	s	sw	s	sw	s	i
Methylene chloride	s	s	s	s	sw,f	s
MIBK	s	s	s	s	i	s
THF	s	s	s	s	sw	s
Toluene	s	s	s	s	i	s

[a] s=soluble; i=insoluble; sw=swells; f=floats

TABLE 11

SOLUBILITIES OF METHYL AND BUTYL ACRYLATE COPOLYMERS[a]

Solvent	25% MA	50% MA	75% MA	25% BA	50% BA	75% BA
Acetone	i	sw	sw	i	sw	sw
Acetonitril	i	i	sw	i	i	sw
Benzene	i	i	sw	i	i	sw
Butyl acetate	i	i	sw	i	sw	sw
Butyl alcohol	i	i	sw	i	sw	sw
γ-Butyrolactone	sw	sw	sw	i	sw	sw
Carbon tetrachloride	i,f	i	sw,f	i,f	i,f	sw,f
Cellosolve acetate	i	sw	sw	i	sw	sw
Chloroform	sw	sw,f	sw,f	sw,f	sw	sw,f
1,4-Dioxane	sw	sw	sw	i	sw	sw
DMSO	sw	sw	sw	sw	sw	sw
Ethyl acetate	i	i	sw	i	sw	sw
Ethyl ether	i	i	i	i	i	sw
n-Heptane	i	i	i	i	i	i
MEK	i	i	sw	i	sw	sw
Methyl cellosolve	i	sw	sw	sw	sw	sw
Methylene chloride	i	i	sw	i	sw	sw,f
MIBK	i	i	sw	i	sw	sw
THF	sw	sw	sw	i	sw	sw
Toluene	i	sw	sw	i	i	i

[a] i=insoluble; sw=swells; f=floats

TABLE 12

SOLUBILITIES OF METHYL METHACRYLATE AND BUTYL METHACRYLATE COPOLYMERS~

Solvent	25%MMA	50%MMA	75%MMA	25%BMA	50%BMA	75%BMA
Acetone	i	i	sw	i	Sw	sw
Acetonitrile	i	i	sw	i	i	sw
Benzene	i	i	sw	i	i	SW
Butyl acetate	i	i	i	i	sw	SW
Butyl alcohol	i	i	i	i	sw	SW
γ-Butyrolactone	i	SW	sw	sw	sw	sw
Carbon tetrachloride	i,f	i,f	sw,f	i,f	i,f	sw,f
Cellosolve acetate	i	sW	sw	i	sw	sw
Chloroform	i,f	sw,f	sw,f	sw,f	sw,f	sw,f
1,4-Dioxane	i	SW	sw	i	sw	sw
DMSO	i	SW	sw	sw	sw	sw
Ethyl acetate	i	i	sw	i	sw	sw
Ethyl ether	i	i	i	i	i	sw
n-Heptane	i	i	i	i	i	i
MEK	i	i	sw	i	sw	sw
Methyl cellosolve	i	SW	sw	sw	sw	sw
Methylene chloride	i	i	sw	sw	sw	sw,f
MIBK	i	i	sw	i	sw	sw
THF	i	sw	sw	sw	sw	sw
Toluene	i	i	sw	i	i	sw

[a] i=insoluble; sw=swells; f=floats

TABLE 13

SOLUBILITIES OF STEAROYL METHACRYLATE AND HYDROXYETHYL METHACRYLATE COPOLYMERS

Solvents	25%StMA	50%StMA	75%StMA	25%HEMA	50%HEMA	25%HEMA
Acetone	sw	sw	sw	i	i	sw
Acetonitrile	i	i	i	i	i	i
Benzene	sw	sw	sw	i	i	i
Butyl acetate	sw	sw	s	i	i	i
Butyl alcohol	sw	sw	sw	i	i	i
γ-Butyrolactone	sw	sw	sw,f	sw	sw	sw
Carbon tetrachloride	sw,f	sw,f	i	i,f	i,f	i,f
Cellosolve acetate	sw	sw	sw	i	i	i
Chloroform	sw,f	sw,f	i,f	i	i,f	i,f
1,4-Dioxane	sw	sw	s	i	sw	sw
DMSO	sw	sw	sw,f	sw	sw	sw
Ethyl acetate	sw	sw	sw	i	i	i
Ethyl ether	sw	sw	s	i	i	i
n-Heptane	i	sw	i	i	i	i
MEK	sw	sw	s	i	i	i
Methyl cellosolve	sw	sw	i	sw	sw	sw
Methylene chloride	sw,f	sw,f	i	i	i	i
MIBK	sw	sw	s	i	i	i
THF	sw	sw	s	i	sw	sw
Toluene	sw	sw	i,f	i	i	i

[a] s=soluble; i=insoluble; sw=swells; f=floats

all the nitrogen present in the sample was due to intact EMCF, and only the comonomer was present. For example, for 50% methyl acrylate:

Calculated nitrogen content:	13.39%
Observed nitrogen content:	10.89%
Nitrogen content in EMCF:	14.73%
Recalculated EMCF content=	$\frac{10.89}{14.73}$ = .7393 or 73.93% EMCF

The results of elemental analysis and these calculations can be seen in Tables 14–25.

Hydrolysis Studies

Once the EMCF, its homopolymer, and copolymers were prepared it was desired that the relative release rate of 5–FU from each be determined. Time limited the study to 5–FU, EMCF, poly(EMCF), the methyl acrylate copolymers, and the butyl acrylate copolymers. The other copolymers are left to future studies. Pulverized samples sieved to be in the 40 to 70 mesh particle size range were used. Comparison studies using this powder from EMCF or its homopolymer compressed into pellets measuring 12.7 mm in diameter by 3.5 mm in height under 1000 pounds per square inch were also done. All samples in this study were exactly 0.5000g.

The dissolution apparatus (see Figure 26) was modeled after several found in literature.[124,154,155,156,157,158] A water bath was set to 37.0 $\pm$ 0.1°C. Exactly 1000 ml of deionized water was pipetted into a 1000 ml Erlenmeyer flask using a 100 ml volumetric pipette. This flask was then tightly covered with parafilm, submerged in the water bath up to the top of the water line in the flask, and held in

CALCULATED VS. OBSERVED VALUES OF ELEMENTAL ANALYSIS OF EMCF

Element	Calculated	Observed
C	46.32	56.58
H	4.24	4.12
N	14.73	14.30
and F	34.71	35.00

TABLE 15

CALCULATED VS. OBSERVED VALUES OF ELEMENTAL ANAYLSIS OF THE POLYMER CHANGED AS 100% EMCF

Element	100% EMCF	17.79% $C_6H_{10}O_2$:82.21% EMCF	Observed
C	46.32	47.93	47.51
H	4.24	4.87	5.05
N	14.73	12.11	12.11
O and F	34.71	35.10	35.33

TABLE 16

CALCULATED VS. OBSERVED VALUES OF ELEMENTAL ANALYSIS OF COPOLYMER CHARGED AS 25% MOLE% METHYL ACRYLATE(MA): 75 MOLE% EMCF

Element	25%MA:75% EMCF	26.07% MA:73.93% EMCF	Observed
C	47.19	48.79	48.10
H	4.49	4.96	5.40
N	13.39	10.89	10.89
O and F	34.93	35.35	35.61

CALCULATED VS. OBSERVED VALUES OF ELEMENTAL ANAYLSIS OF COPOLYMER CHARGED AS 50 MOLE% METHYL ACRYLATE(MA): 50 MOLE% EMCF

Element	50% MA:50% EMCF	35.23% MA:64.77% EMCF	Observed
C	48.52	49.66	49.09
H	4.89	5.22	5.65
N	11.32	9.54	9.54
O and F	35.28	35.57	35.72

TABLE 18

CALCULATED VS. OBSERVED VALUES OF ELEMENTAL ANALYSIS OF COPOLYMER CHARGED AS 75 MOLE% METHYL ACRYLATE(MA): 25 MOLE% EMCF

Element	75% MA:25% EMCF	49.83% MA:50.17% EMCF	Observed
C	50.83	51.05	50.76
H	5.56	5.62	5.97
N	7.73	7.93	7.39
O and F	35.87	35.93	35.88

CALCULATED VS. OBSERVED VALUES OF ELEMENTAL ANALYSIS OF COPOLYMER CHARGED AS 25 MOLE% BUTY ACRYLATE(BA):75 MOLE% EMCF

Element	25% BA:75% EMCF	27.77% BA:72.23% EMCF	Observed
C	48.83	51.67	49.24
H	4.92	5.68	5.70
N	12.81	10.64	10.64
O and F	33.44	32.00	34.42

TABLE 20

CALCULATED VS OBSERVED VALUES OF ELEMENTAL ANAYLSIS OF COPOLYMER CHARGED AS 50 MOLE% BUTYL ACRYLATE (BA):50 MOLE% EMCF

Element	50% BA:50% EMCF	38.49% BA:61.51% EMCF	Observed
C	52.30	53.74	52.14
H	5.85	6.24	6.24
N	10.16	9.06	9.06
O and F	31.69	30.96	32.56

TABLE 21

CALCULATED VS OBSERVED VALUES OF ELEMENTAL ANALYSIS OF COPOLYMER CHARGED AS 75 MOL% BUTYL ACRYLATE (BA):25 MOLE% EMCF

Element	75% BA:25% EMCF	59.54% BA:40:46% EMCF	Observed
C	57.39	57.80	57.05
H	7.22	7.34	7.36
N	6.27	5.96	5.96
O and F	29.12	28.91	29.63

CALCULATED VS. OBSERVED VALUES OF ELEMENTAL ANALYSIS OF COPOLYMER CHARGED AS 50 MOLE% METHYL METHACRYLATE (MMA):50 MOLE% EMCF

Element	50% MMA:50% EMCF	39.68% MMA:60.32% EMCF	Observed
C	49.87	51.74	50.84
H	5.23	5.75	5.99
N	10.91	8.89	8.89
O and F	33.99	33.62	34.28

CALCULATED VS. OBSERVED VALUES OF ELEMENTAL ANALYSIS OF COPOLYMER CHARGED AS 50 MOLE% BUTYL METHACRYLATE (BMA):50 MOLE% EMCF

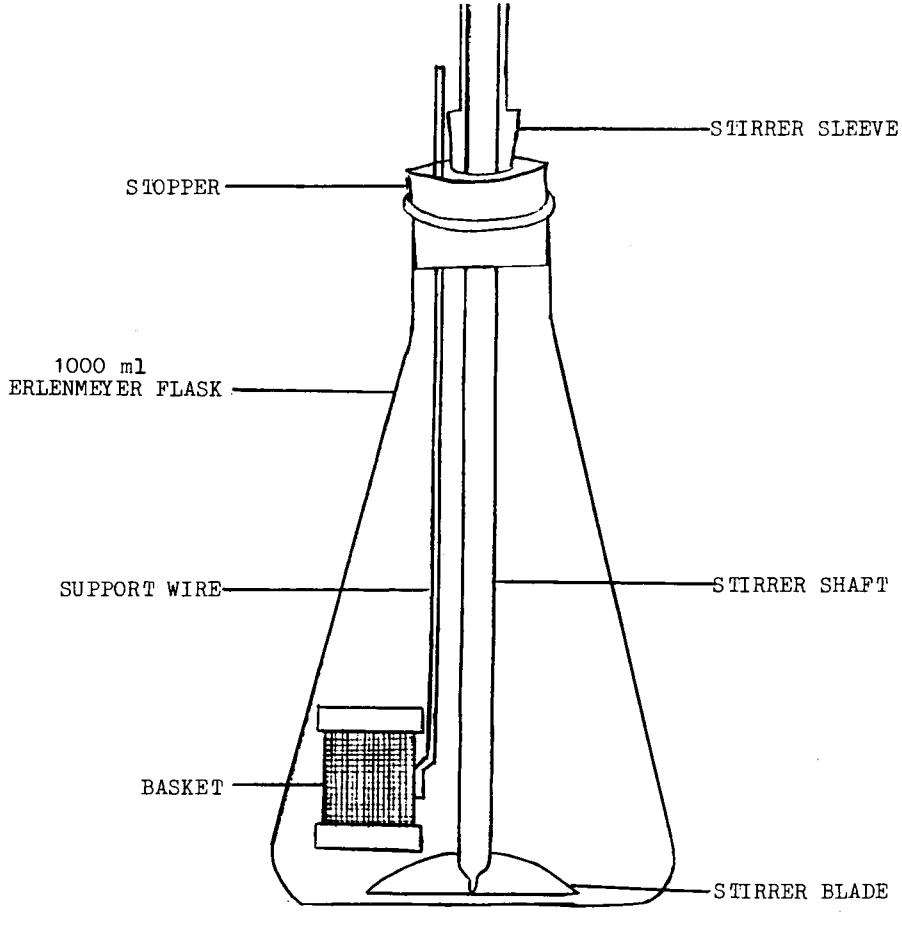
Element	50% BMA:50% EMCF	43.92% BMA:56.08% EMCF	Observed
C	53.39	55.65	53.90
H	6.13	6.73	6.73
N	9.83	8.26	8.26
O and F	30.65	29.34	31.11

CALCULATED VS. OBSERVED VALUES OF ELEMENTAL ANALYSIS OF COPOLYMER CHARGED AS 50 MOLE% STEAROYL METHACRYLATE (StMA):50 MOLE% EMCF

Element	50% StMA:50% EMCF	58.11%StMA:41.89% EMCF	Observed
C	63.54	65.03	62.96
H	8.73	8.74	8.96
N	6.74	6.17	6.17
O and F	20.99	20.07	21.91

CALCULATED VS. OBSERVED VALUES OF ELEMENTAL ANALYSIS OF COPOLYMER CHARGED AS 50 MOLE% HDYROXYETHYL METHACRYLATE (HEMA):50 MOLE% EMCF

Element	50% HEMA:50% EMCF	59.13% HEMA:40.87% EMCf	Observed
C	49.28	51.67	49.51
H	5.11	6.31	6.24
N	10.14	6.02	6.02
O and F	35.47	35.99	38.23



DISSOLUTION APPARATUS

Figure 26.

place with a clamp for 24 hours before starting the experiment so the flask and contents would equilibrate to temperature.

After submerging the flask, 7-8 ml. of hot wax was poured into a 50 ml. beaker. The end of an opened 6 cm. in length by 2.5 cm. in diameter cellulose dialysis membrane was immediately placed into this wax and the wax was allowed to harden overnight. The wax with the embedded membrane was freed from the beaker using a microspatula, and a square sample port was cut into the wax inside the dialysis membrane, also using a microspatula. The wax embedded membrane was then placed with the wax portion on top into a 4.00 cm. high by 2.75 cm. in diameter stainless steel cage to which a stainless steel support wire was soldered. The junction between the cage and wax was carefully sealed by applying hot wax through a Pasteur pipette and then a cool flame was applied to insure a good seal. The dialysis membrane was then trimmed off to be even with the bottom of the cage.

A 70 mesh stainless steel screen cut to the dimensions of the bottom of the cage was placed into a 50 ml. beaker along with 5 ml. of hot wax. The cage assembly was lowered into this, making sure that the 70 mesh screen was exactly over the bottom of the cage. After the wax hardened, the assembly was removed from the beaker by running a microspatula around the edge of the wax and heating the bottom of the beaker on a hot plate if necessary. The top and bottom wax seals were trimmed so that the assembly could fit into a 1000 ml. Erlenmeyer flask (See Figure 27). A rubber stopper for the flask which had two holes bored into it, one in the center to accommodate the sleeve of a mechanical stirrer and the other off center to accommodate the support wire, was placed on the support wire.

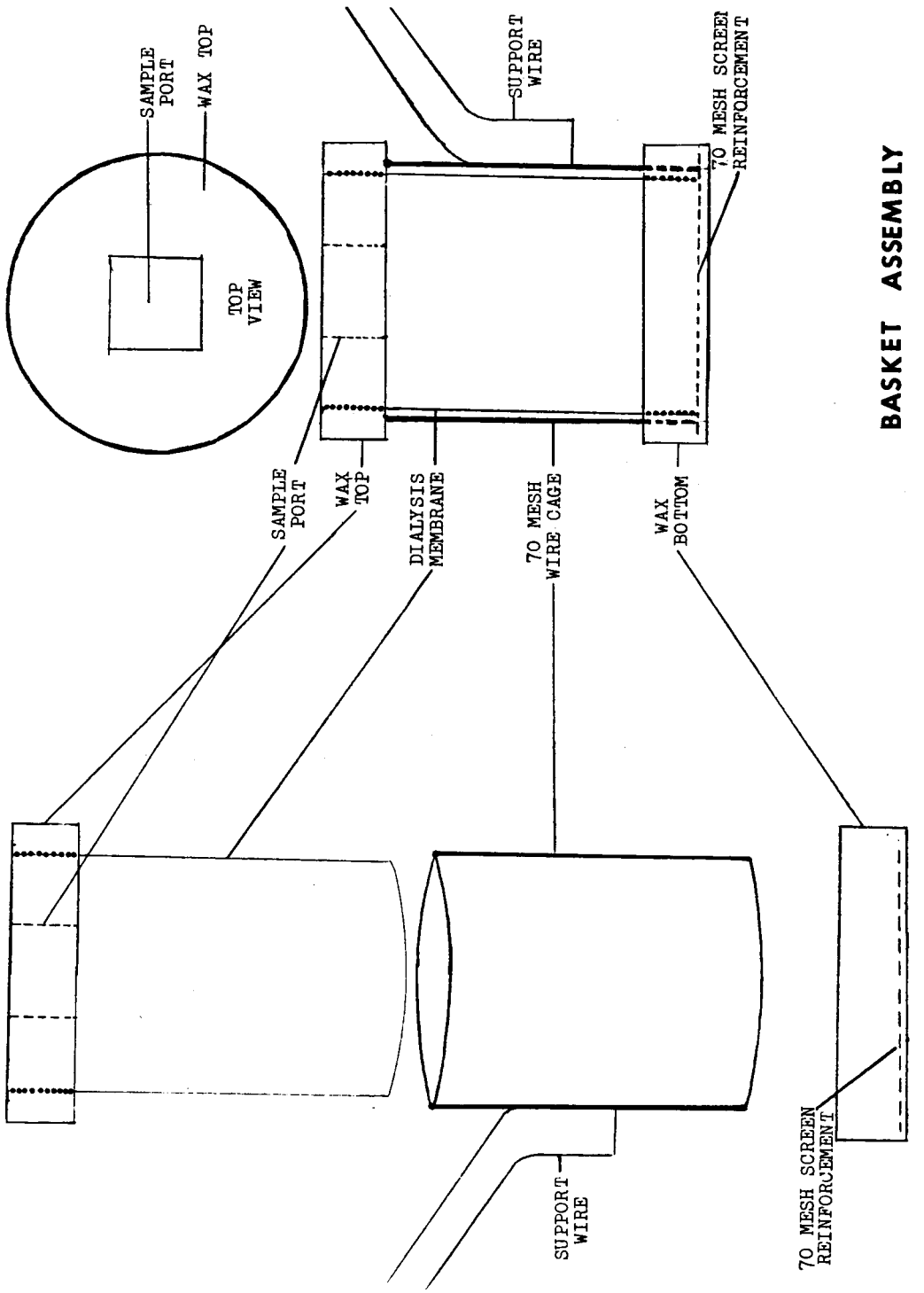

BASKET ASSEMBLY
SAMPLE PORT
WAX TOP
TOP VIEW
SUPPORT WIRE
70 MESH SCREEN REINFORCEMENT
SAMPLE PORT
WAX TOP
DIALYSIS MEMBRANE
70 MESH WIRE CAGE
WAX BOTTOM
SUPPORT WIRE
70 MESH SCREEN REINFORCEMENT

Figure 27.

One hour prior to starting a run, the sample was introduced into the cage assembly through the sample port. A round 70 mesh stainless steel screen was placed over the sample port and the top carefully flamed so as not to melt the wax too much and cause it to drip into the cage onto the sample. When the screen was partially embedded into the wax using a slight pressure, hot wax was placed over it using a Pasteur pipette, leaving a small hole about 5 mm. in diameter over the center of the sample port. The wax hardened, sealing the screen into place (See Figure 28). The stopper was then wrapped in parafilm.

At the start of the trial, the cage assembly was submerged into the Erlenmeyer flask containing the water equilibrated to 37.0°C. Using a long Pasteur pipette, water from the flask was gently forced into the cage assembly through the small hole in the top, expelling the air. The opening was then sealed off with hot wax while holding the assembly so that the screen in the opening was at the water level in the flask. After a few moments, the wax hardened and the assembly was submerged into the flask while putting the stopper into place. The mechanical stirrer was introduced into the flask through the hole in the center of the stopper and the sleeve of the stirrer pressed tightly into place. A clamp was used to prevent the sleeve from moving. The medium was then stirred at 260 rpm.

Samples were removed at regular intervals from the flask by sliding the sleeve up on the stirrer shaft and using a Pasteur pipette to withdraw 3 ml. of the medium. These samples were then assayed for 5-FU on a Cary 14 spectrophotometer at 265 nm. The test samples were then returned to the reaction vessel through the opening in the stopper and the stirrer sleeve clamped back into place.

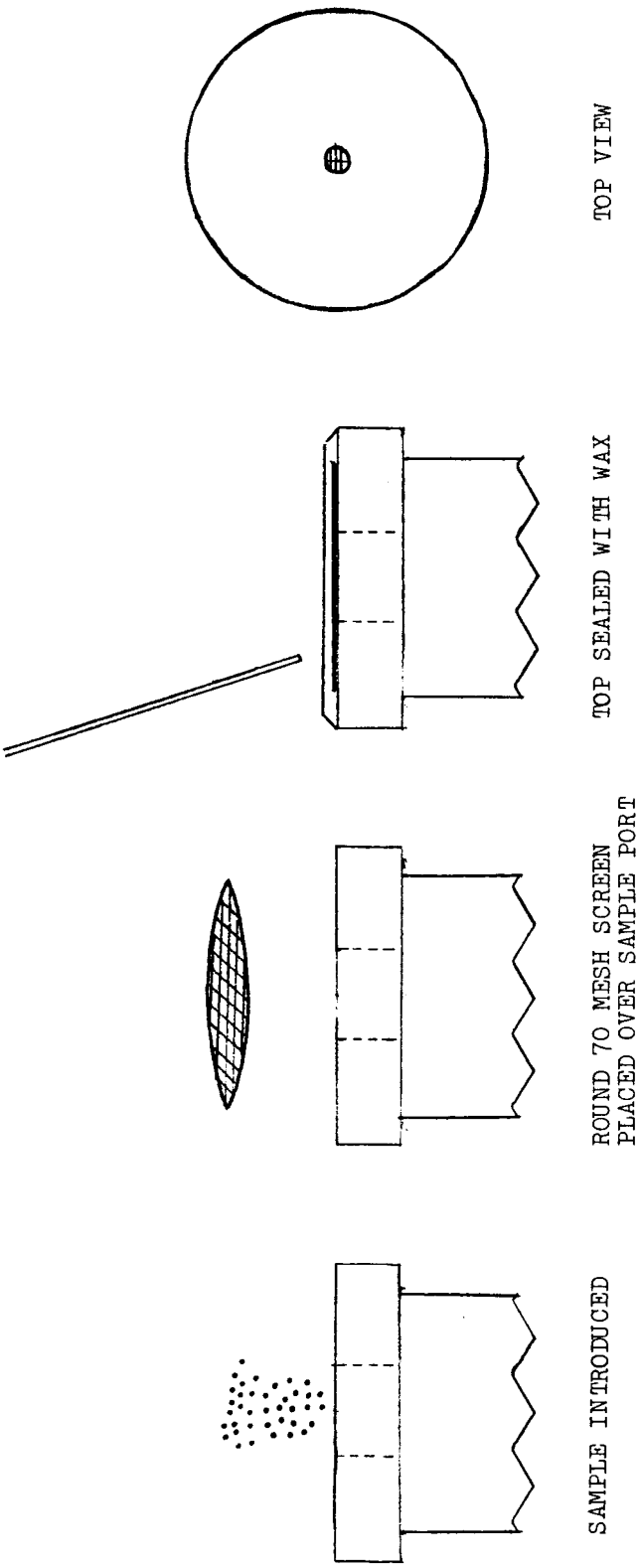


Figure 28. Introducing the sample and sealing the basket assembly.

All hydrolysis trials, except those on the pellets, were run in at least duplicate and usually at different times. A detailed report of the data obtained in these studies can be found in Appendix A. The trial numbers do not reflect the order in which they were run.

CHAPTER IV

RESULTS AND DISCUSSION

It was the purpose of this work to prepare polymerizable derivatives of 5-fluorouracil, uracil, and piperidine with isocyanato-ethyl methacrylate and to polymerize them. The structure of 1-(N-2-ethylmetharylcarbamoyl)-5-fluorouracil was supported by its IR spectrum, elemental analysis, polymerizability, release of 5-FU upon hydrolysis, and the similarity in the IR spectrum with that of both 1-(N-2-ethylmethacrylcarbamoyl)uracil and 1-(N-2-ethylmethacry·lcarbam-oyl)piperidine. Assignment of the peaks indicating the desired products can be seen in Table 26. Support of homopolymerization of these three monomers comes from changes in solubility, changes in appearance, and differences in their IR spectra from the corresponding monomers. Each of the IR spectra of these polymers resembled the other two, in some features.

The 5-FU derivative was also copolymerized with methyl acrylate, butyl acrylate, methyl methacrylate, butyl methacrylate, stearoyl methacrylate, and hydroxyethyl methacrylate in 25/75, 50/50, 75/25 mole% ratios. Elemental analysis revealed that the compositions of the copolymers were different from the charged mole ratios of the mono-mers. Infrared analysis did confirm the expected qualitative order within each group of copolymers, as did elemental analysis when the whole group was tested. For example, the methyl acrylate copolymers were not 25, 50, and 75 mole% methyl acrylate, but rather 26.07, 35.23, and 49.83 mole% as shown by elemental analysis. Table 27 gives a complete listing of these results. The IR specrum of each of these

TABLE 26

IR PEAKS INDICATING THE DESIRED PRODUCTS

Product	Peak Frequency (cm^{-1})	Assignment
1-(N-2-ethylmethacrylcarbamoyl)-5-Flourouracil	3330	assymetric N-H
	3180 and 3070	symmetric N-H
	1740 to 1600	>C=O stretch, Amide I
	1510	Amide II
	1330	Amide III
	1275	C-F stretch
	910 and 940	C-H out of plane bend
1-(N-2-ethylmethacrylcarbamoyl)-5-Fluorouracil	3310	assymetric N-H
	3150 and 3090	symmetric N-H
	1750 to 1600	>C=O stretch, Amide I
	1510	Amide II
	1327	Amide III
	950	>C-H out of plane bend

TABLE 27

ACTUAL % OF EMCF IN COPOLYMERS

Comonomer	Theoretical % EMCF 25	50	75
Methyl Acrylate	50.17	64.77	73.93
Butyl Acrylate	40.46	61.51	72.23
Methyl Methacrylate	-	60.32	-
Butyl Methacrylate	-	56.08	-
Stearoyl Methacrylate	-	41.89	-
Hydroxyethyl Methacrylate	-	40.87	-

showed an increase in relative magnitude of the peaks due to methyl acrylate as compared to a decrease in relative magnitude of the peaks due to EMCF as the copolymers increased in methyl acrylate content. This was also seen in the other groups of copolymers.

The difference in theoretical and actual analysis of the homopolymer and copolymers may be explained by three considerations. The first is that the reactivity of the comonomers with EMCF was different than EMCF with itself, and the comonomers may not have reacted at all or formed short, soluble chains with themselves. Either of these would have been washed away during the methanol washes. The second possibility is that a "deblocking" reaction, where the EMCF reverts back to 5-FU and IEM, could have occurred. In this case the IEM may cyclic trimerize to a soluble product leaving insoluble 5-FU. The third possibility is that EMCF may have cyclic trimerized to a soluble product.

The "deblocking" reaction may explain the sudden release of 5-FU initially in some of the copolymers since any free 5-FU present would rapidly dissolve. Crosslinking could also have occurred through these "deblocked" isocyanate groups which would explain the homopolymer and most of the copolymers being insoluble or only swelling in the solvents in which they were tested. The only copolymer soluble was the one charged as 75 mole% StMA. The long side chain would keep two chains or different parts of the same chain apart so that free isocyanate groups could not react, and this would explain its solubility.

Graphs of the data from hydrolysis studies on EMCF, poly[EMCF], the methyl acrylate copolymers, and the butyl acrylate copolymers are shown in Figures 29, 30, 31, 32, and 33. Figure 29 shows the very rapid solution of 5-FU as compared to the monomer and the slow rate of release from the polymer pellet, which was also slower than the polymer powder. Reproducible results were obtained using this method of study which is emphasized by the four separate runs of the monomer graphed here.

Figure 30 compares the release rates of the monomer and polymer powders. The polymer is shown to release 5-FU more slowly than the monomer. Umrigar, Ohashi, and Butler found the same results with their monomer and homopolymer, but both hydrolyzed too rapidly to be of practical use.[17] After 50 hours, however, the polymer began to release 5-FU very rapidly, as can be seen from the data in Appendix A. It should be noted that 3 of the trials (8-10) with the polymer powder were dismissed on the basis that the polymer powder should not release 5-FU faster than monomer. In trial 7, the polymer had not been ground with a mortar and pestle yet. The monomer pellet released 5-FU more slowly than the monomer itself initially as would be expected from the results

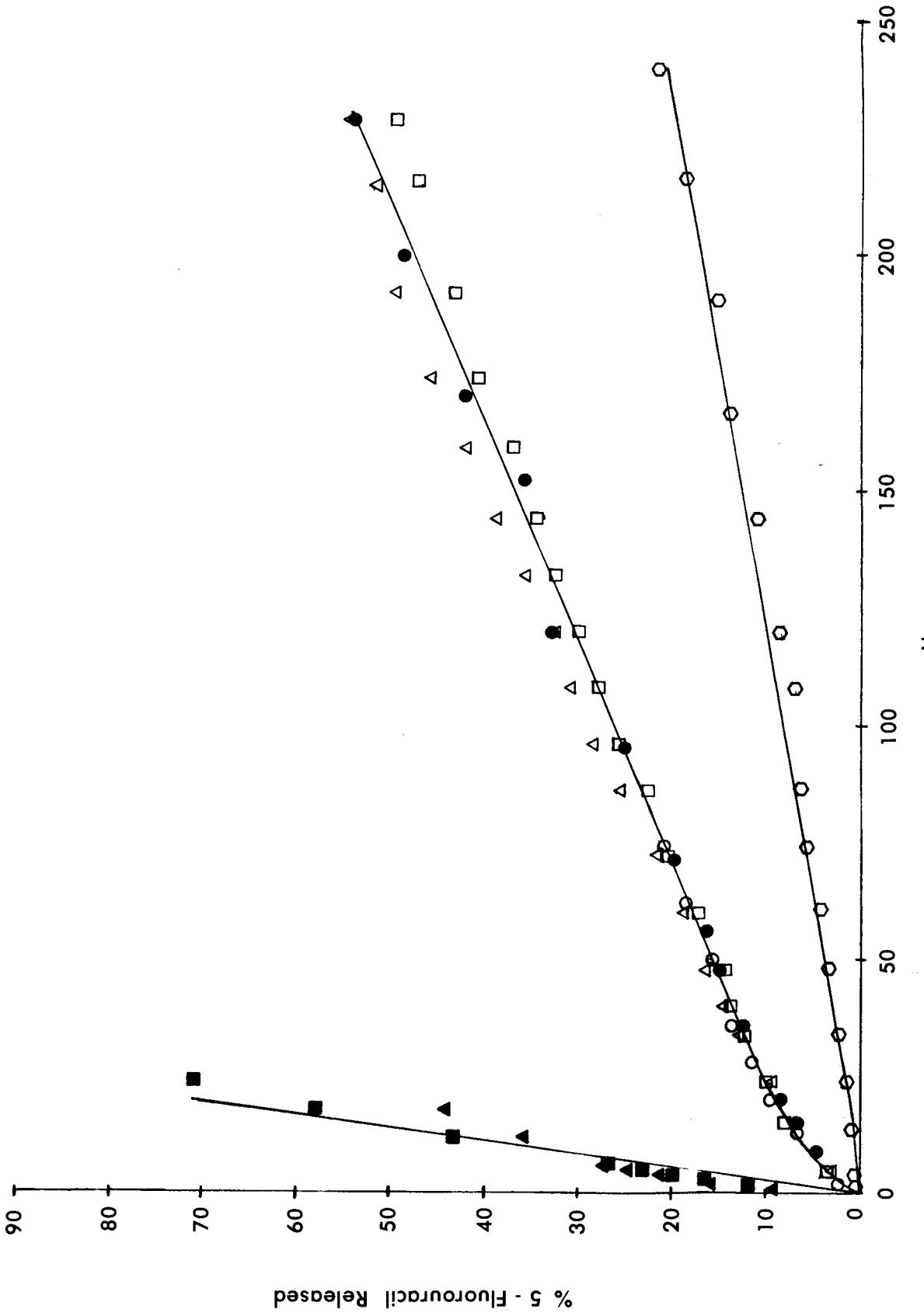
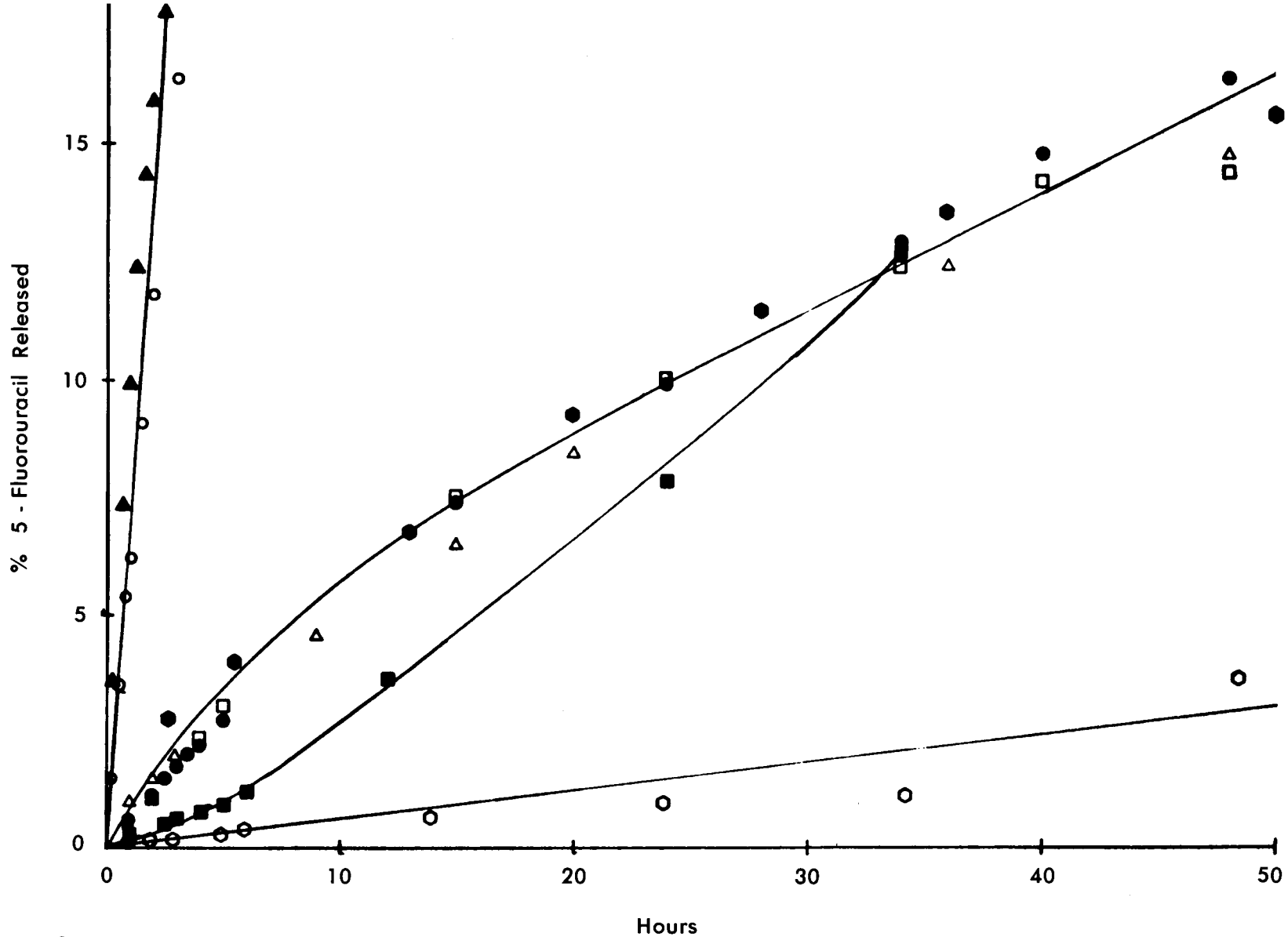


Figure 29- Release of 5-FU from its crystals (▲,■), EMCF (△,□,○,●), and the polymer pellet (○).



gure 30- Release of 5-FU from its crystals (○,▲), EMCF (●,⬢,△,□), the EMCF pellet (■), and poly[EMCF] (○).

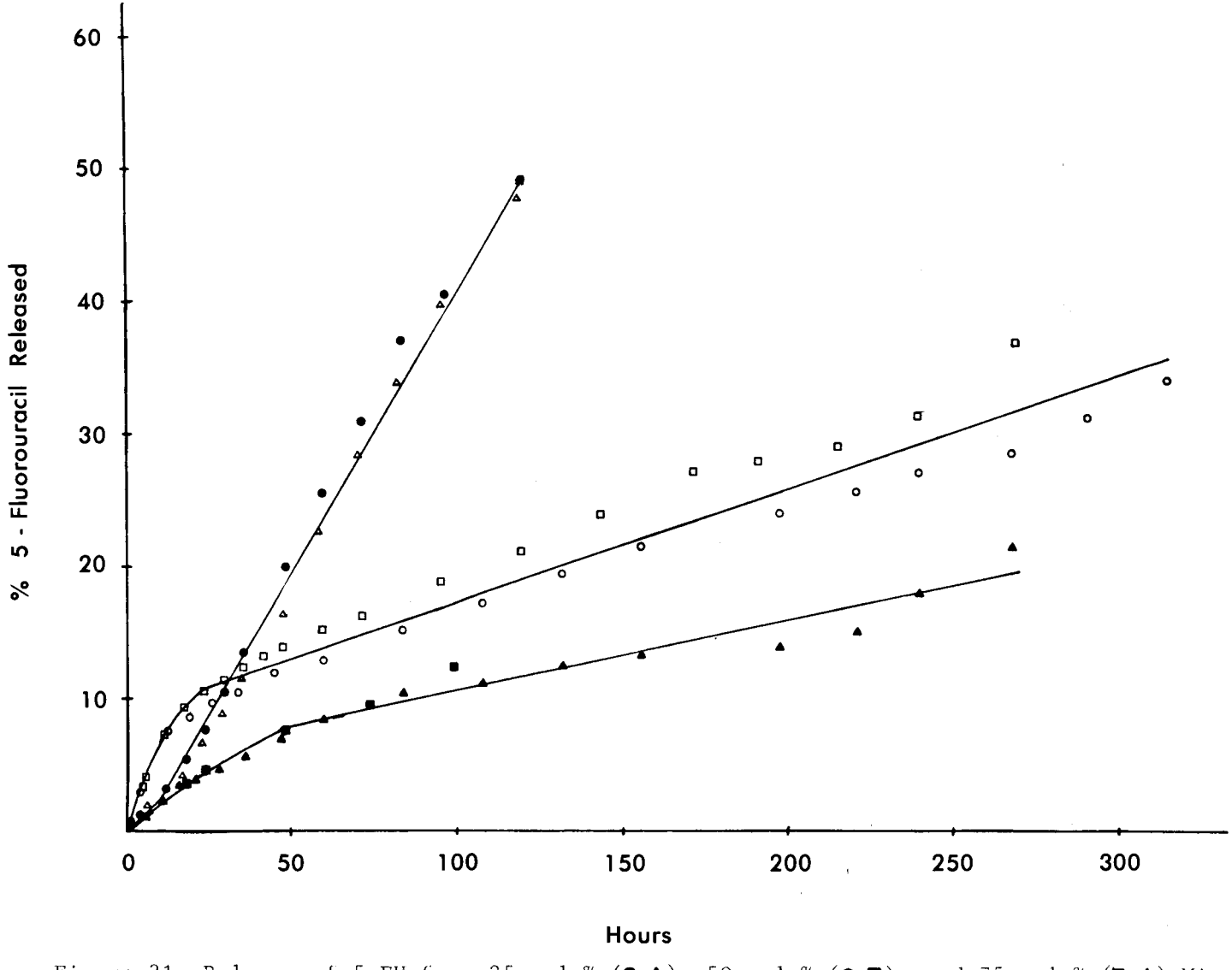


Figure 31-- Release of 5-FU from 25 mole% (●,▲), 50 mole% (○,□), and 75 mole% (■,▲) MA c

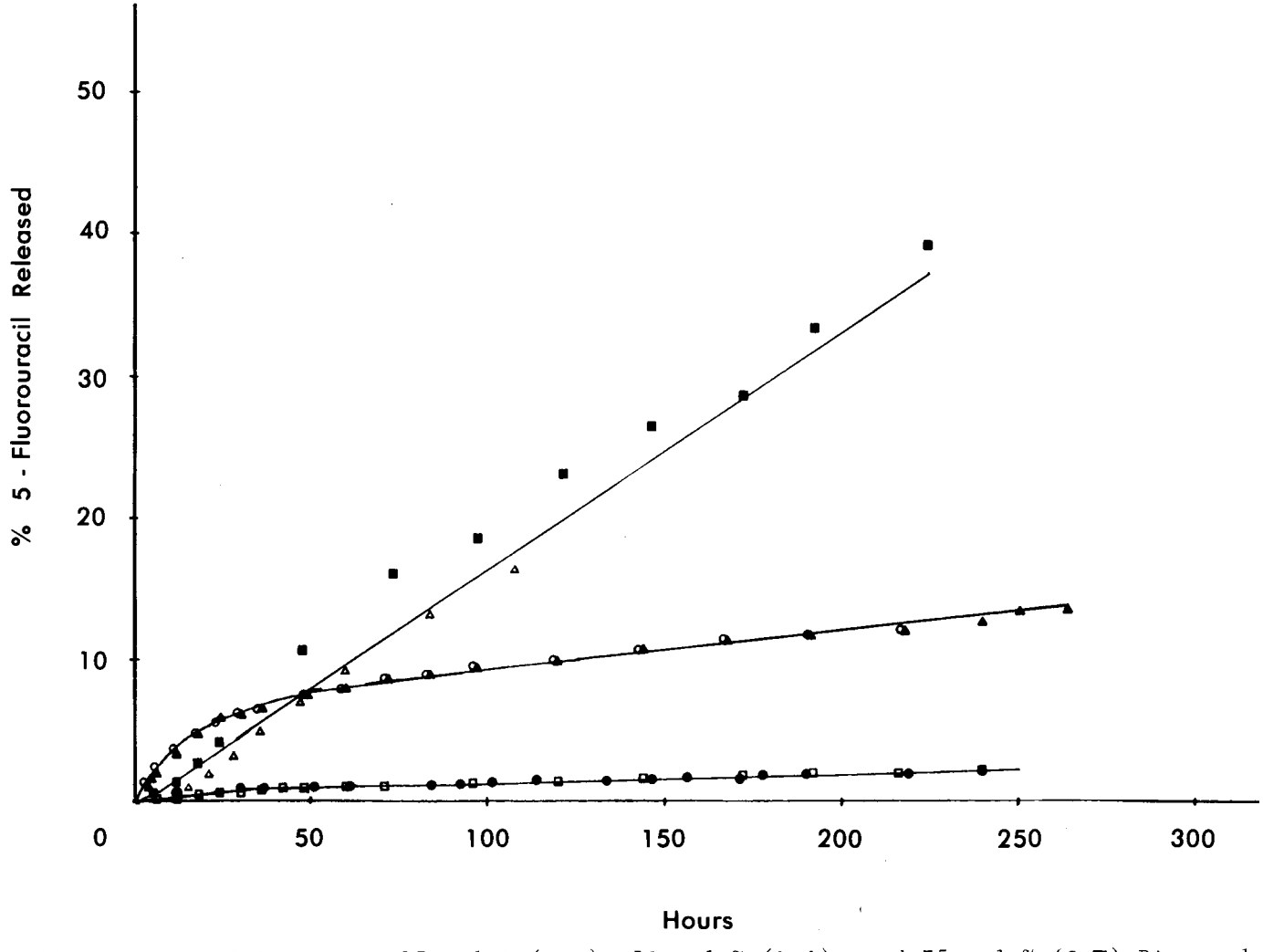


Figure 32- Release of 5-FU from 25 mole% (■,△), 50 mole% (○,▲), and 75 mole% (●,□) BA copolymers.

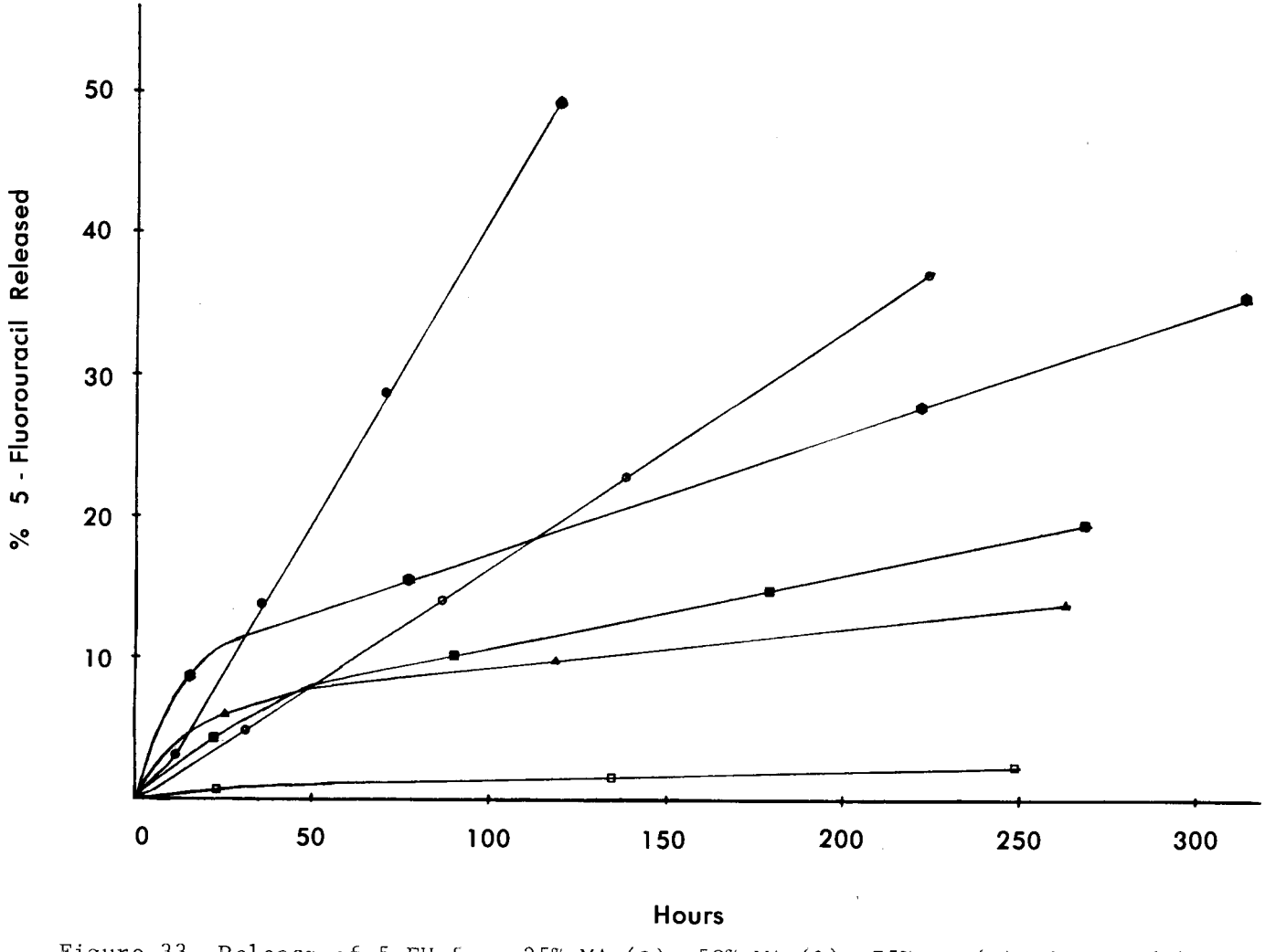


Figure 33- Release of 5-FU from 25% MA (●), 50% MA (⬢), 75% MA (■), 25% BA (○), 50% BA (▲), 75% BA (□) copolymers. The symbols are only for identification only and are not data points.

obtained with polymer pellet and as compared to work done by Kaetsu, Yoshida, and Yamada on matrix encapsulated systems of various shapes.[148] The release rate then surpassed that of the monomer. This may be due to degradation of the monomer in the interior of the pellet while it is under pressure. Further research is required to explain both the release rate from the polymer powder and the release rate of the monomer pellet in comparison to the monomer powder.

Figure 31 shows the release rates of the methyl acrylate copolymers, and Figure 32 shows the release rates of the butyl acrylate copolymers. It can be seen that as the comonomer content of the polymer increases, the release rate of 5–FU decreases. This is due to the increased hydrophobicity of the copolymer with increased comonomer content, inhibiting diffusion of water into the matrix and subsequent diffusion of 5–FU out of the matrix. The same type of occurrence was was found by several other researchers using their systems.[147,148,150] Figure 33 further emphasizes that as the hydrophobicity of the matrix increases, the release rate of 5–FU decreases. Methyl acrylate co–polymers release 5–FU much faster than those of the same mole% of butyl acrylate. All have zero order release rates, however.

A system cited by Levowitz et al also has a zero order release rate for 5–FU.[103] The device consists of an implantable hollow cylinder made of Hydron plugged at both ends with adhesive containing the imput and output catheters and ensheathed in a nylon jacket with various window configurations. The drawbacks to this system as opposed to a system which could be totally implanted, such as the copolymers cited in this thesis, include the need for tubes perforating the skin, lack of mobility during treatment, increased patient participation, and the need for professional monitoring of the device.

Kaetsu et al have made a matrix device by placing 5–FU into monomer and then polymerizing by radiation at -78°C. The resulting matrix released 5–FU according to Higuchi kinetics. The amount of 5–FU delivered by this type of device would, therefore, not be constant in dose. Also, matrix encapsulated systems could not be easily formed as powders, discs, pellets, or any desired shape or size, as a polymeric drug could be.

The most important result of these studies is that, after a short induction period, each of the copolymers utilizing EMCF shows a zero order release rate which can be controlled by choice of comonomer and its relative concentration in the charge. The significance of a zero order release rate is that a constant therapeutic level of drug can be delivered to the target site for an extended period of time with diminished side effects from the drug. A device made of these copolymers could be made in any desired shape and be totally implanted at the site of treatment.

CHAPTER V

SUMMARY

The reactions of 5-fluorouracil, uracil, and piperidine with isocyanatoethyl methacrylate were studied using 1,4-dioxane as the solvent. An IR spectum was taken on each product and new peaks were found in each case, indicating synthesis of the desired product. The products were: 1) 1-(N-2-ethylmethacrylcarbamoyl)-5-fluorouracil, 2) 1-(N-2-ethylmethacrylcarbamoyl)uracil, and 3) 1-(N-2-ethylmethacryl-carbamoyl)piperidine. These were polymerized, which was confirmed by their change in appearance, IR spectra, and solubility. The 5-fluorouracil derivative was also copolymerized with 25, 50, and 75 mole% of each: 1) methyl acrylate, 2) butyl acrylate, 3) methyl meth-acrylate, 4) butyl methacrylate, 5) stearoyl methacrylate, and 6) hydroxyethyl methacrylate. Copolymerization occurred at these mole percentages with each of these comonomers as confirmed by IR analysis and changes in solubility of the products as compared to reactants, but elemental analysis revealed the products not to contain the mole ratios as that of the charge. All of the homopolymers and copolymers of the derivatives except the copolymer charged as 75 mole% stearoyl meth-acrylate:25 mole% EMCF were insoluble in the solvents tested.

Hydrolysis studies revealed that the polymer hydrolyzes more slowly than the monomer up to 50 hours, and that the tablets of each release 5-FU more slowly than the corresponding powders. Studies with the copolymers of methyl acrylate and butyl acrylate show that as the hydrophobicity of the matrix increases, the release rate of 5-FU from the copolymer decreases. Zero order release rates were observed in

these systems, which makes them good candidates for further study since controlled release chemotherapy is dependent upon this type of behavior. With zero order release rates, a constant level of drug is delivered to the target site. The release can be controlled by the amount and type of comonomer in the copolymer, which determines the hydrophobicity of the copolymer. Shape of the material also affects release rate of 5-FU from the system. These copolymers show promise as controlled release systems for 5-fluorouracil in localized antineoplastic chemotherapy, but further research is needed before this goal is reached.

Future research should include elemental analysis of the copolymers charged as 25 mole% and 75 mole% methyl methacrylate, butyl methacrylate, stearoyl methacrylate, and hydroxyethyl methacrylate. Hydrolysis studies on the groups of methyl methacrylate, butyl methacrylate, stearoyl methacrylate, and hydroxyethyl methacrylate are needed. More research on the possible "deblocking" reaction of EMCF should be conducted. NMR studies on the soluble stearoyl methacrylate may be revealing. And biological studies using these copolymers is necessary to ascertain if side effects are reduced and localized therapy attained by their use.

APPENDIX A

Data From Hydrolysis Studies

DATA FROM HYDROLYSIS STUDIES

Trial 1 – 5-Fluorouracil

Time (hours)	Dilution	Optical Density	% 5-FU Released
0.25	None	0.410	1.49
0.50	None	0.940	3.49
0.75	None	1.425	5.31
1.00	10X	0.180	6.19
1.50	10X	0.255	9.03
2.00	10X	0.330	11.8
3.00	10X	0.450	16.4
4.00	10X	0.550	20.1
5.00	10X	0.630	23.1
6.00	10X	0.725	26.7
12.00	10X	1.160	43.1
18.00	10X	1.550	57.8
24.00	10X	1.930	72.1
60.00	100X	0.270	95.9
75.00	100X	0.270	95.9
99.00	100X	0.270	95.9

Trial 2 – 5-Fluorouracil

Time (hours)	Dilution	Optical Density	% 5-FU Released
0.33	None	0.920	3.41
0.67	None	1.960	7.31
1.00	10X	0.280	9.93
1.33	10X	0.345	12.4
1.67	10X	0.395	14.3
2.00	10X	0.440	16.0
2.50	10X	0.490	17.9
3.50	10X	0.560	20.5
4.00	10X	0.580	21.2
5.00	10X	0.670	14.6
6.00	10X	0.740	17.3
12.00	10X	0.970	35.9
18.00	10X	1.190	44.2

DATA FROM HYDROLYSIS STUDIES (CON'T)

Trial 3 - EMCF

Time (hours)	Dilution	Optical Density	% 5-FU Released
0.25	None	0.040	0.37
0.50	None	0.070	0.54
0.75	None	0.085	0.60
1.00	None	0.145	1.07
2.00	None	0.205	1.56
3.00	None	0.250	1.94
4.00	None	0.310	2.43
9.00	None	0.570	4.58
15.00	None	0.800	6.51
20.00	None	1.040	8.45
36.00	10X	0.165	12.4
48.00	10X	0.195	14.8
56.00	10X	0.215	16.4
71.00	10X	0.255	19.8
95.00	10X	0.320	25.2
120.00	10X	0.410	32.6
152.00	10X	0.450	35.9
175.00	10X	0.525	42.1
200.00	10X	0.605	48.7
229.00	10X	0.650	54.1

Trial 4 - EMCF

Time (hours)	Dilution	Optical Density	% 5-FU Released
0.33	None	0.170	1.28
0.67	None	0.190	1.44
1.00	None	0.210	1.61
1.33	None	0.255	1.98
2.00	None	0.310	2.43
2.50	None	0.355	2.80
5.50	None	0.495	3.96
13.00	None	0.830	6.74
20.00	None	1.140	9.30
28.00	None	1.410	11.5
36.00	None	1.670	13.6
50.00	10X	0.205	15.7
62.00	10X	0.240	18.6
74.50	10X	0.270	21.0

DATA FROM HYDROLYSIS STUDIES (CON'T)

Trial 5 - EMCF

Trial (hours)	Dilution	Optical Density	% 5-FU Released
0.25	None	0.060	0.51
0.50	None	0.065	0.53
0.75	None	0.085	0.60
1.00	None	0.090	0.62
1.50	None	0.125	0.91
2.00	None	0.160	1.19
2.50	None	0.200	1.52
3.00	None	0.230	1.77
3.50	None	0.260	2.02
4.00	None	0.285	2.22
5.00	None	0.350	2.76
15.00	None	0.920	7.47
24.00	None	1.220	9.93
34.00	None	1.585	13.0
40.00	None	1.810	14.8
48.00	10X	0.215	16.5
60.00	10X	0.245	18.9
72.00	10X	0.280	21.9
86.00	10X	0.325	25.6
96.00	10X	0.360	28.5
108.00	10X	0.390	30.9
120.00	10X	0.410	32.5
132.00	10X	0.450	35.9
144.00	10X	0.485	38.8
159.00	10X	0.525	42.0
174.00	10X	0.570	45.8
192.00	10X	0.615	49.5
216.00	10X	0.640	51.6
229.00	10X	0.675	54.4
255.00	10X	0.740	59.8

DATA FROM HYDROLYSIS STUDIES CON'T

Trial 6 - EMCF

Time (hours)	Dilution	Optical Density	% 5-FU Released
0.25	None	0.030	0.35
0.50	None	0.040	0.45
0.75	None	0.060	0.62
1.00	None	0.065	0.65
1.50	None	0.120	1.00
2.00	None	0.160	1.19
2.50	None	0.190	1.44
3.00	None	0.230	1.77
3.50	None	0.270	2.10
4.00	None	0.300	2.35
5.00	None	0.380	3.01
15.00	None	0.925	7.53
24.00	None	1.235	10.0
34.00	None	1.520	12.4
40.00	None	1.735	14.2
48.00	10X	0.190	14.4
60.00	10X	0.220	16.9
72.00	10X	0.265	20.6
86.00	10X	0.290	22.7
96.00	10X	0.330	26.0
108.00	10X	0.355	28.0
120.00	10X	0.380	30.1
132.00	10X	0.410	32.6
144.00	10X	0.435	34.6
159.00	10X	0.465	37.1
174.00	10X	0.510	40.9
192.00	10X	0.545	43.7
216.00	10X	0.590	47.4
229.00	10X	0.615	49.5
255.00	10X	0.680	54.9

DATA FROM HYDROLYSIS STUDIES (CON'T)

Trial 7 - poly(EMCF)

Time (hours)	Dilution	Optical Density	% 5-FU Released
0.25	None	0.000	0.00
0.50	None	0.010	0.10
0.75	None	0.010	0.10
1.00	None	0.010	0.10
1.50	None	0.010	0.10
2.00	None	0.015	0.20
2.50	None	0.015	0.20
3.00	None	0.020	0.25
4.00	None	0.020	0.25
5.00	None	0.025	0.30
6.00	None	0.035	0.40
14.00	None	0.080	0.80
24.00	None	0.120	1.00
34.25	None	0.155	1.40
48.50	None	0.380	3.70
60.50	None	0.670	6.60
74.00	None	1.280	12.7
86.50	None	1.600	15.9
96.50	10X	0.205	19.0
108.00	10X	0.245	23.0
120.00	10X	0.280	26.6
144.00	10X	0.310	29.6
166.50	10X	0.440	42.6
190.50	10X	0.555	54.6
216.50	10X	0.595	58.2
240.00	10X	0.635	62.2

Trial 8 - poly (EMCF)

Time (hours)	Dilution	Optical Density	% 5-FU Released
0.33	None	0.015	0.14
0.67	None	0.015	0.14
1.00	None	0.025	0.30
1.33	None	0.035	0.40
2.00	None	0.045	0.50
2.50	None	0.055	0.60
5.50	None	0.120	1.00
13.00	None	0.275	2.15
20.00	None	0.440	3.50
28.00	None	0.700	5.65
36.00	None	1.080	8.73
50.00	None	1.970	16.2
88.00	10X	0.545	43.7
120.00	10X	0.765	61.9

DATA FROM HYDROLYSIS STUDIES (CON'T)

Trial 9 - poly(EMCF)

Time (hours)	Dilution	Optical Denisty	% 5-FU Released
0.33	None	0.010	0.10
0.67	None	0.015	0.14
1.00	None	0.020	0.25
1.33	None	0.030	0.35
1.67	None	0.040	0.45
2.00	None	0.045	0.50
2.50	None	0.050	0.55
3.50	None	0.080	0.80
4.00	None	0.090	0.90
5.00	None	0.115	0.97
6.00	None	0.140	1.25
12.00	None	0.260	2.02
18.00	None	0.410	3.26
24.00	None	0.600	4.83
48.00	10X	0.200	15.2
74.00	10X	0.440	35.1
98.00	10X	0.620	49.9
122.00	10X	0.770	62.3
147.00	10X	0.820	66.4
173.00	10X	0.845	68.5
193.00	10X	0.880	71.4
225.00	10X	1.060	86.2

Trial 10 - poly(EMCF)

Time (hours)	Dilution	Optical Density	% 5-FU Released
0.25	None	0.005	0.05
1.00	None	0.010	0.10
1.50	None	0.025	0.30
3.00	None	0.050	0.45
5.00	None	0.120	1.00
12.00	None	0.350	2.76
24.00	None	0.760	6.16
36.00	None	1.475	12.0
50.00	10X	0.255	19.8
60.00	10X	0.330	26.0
72.00	10X	0.440	35.0
84.00	10X	0.535	42.9
96.00	10X	0.625	50.3
108.00	10X	0.685	55.3
123.00	10X	0.765	61.9
138.00	10X	0.790	64.0
156.00	10X	0.815	66.0
180.00	10X	0.825	66.8
193.00	10X	0.840	68.1

DATA FROM HYDROLYSIS STUDIES (CON'T)

Trial 11 - EMCF pellet

Time (hours)	Dilution	Optical Density	% 5-FU Released
0.25	None	0.000	0.00
0.50	None	0.000	0.00
0.75	None	0.010	0.10
1.00	None	0.020	0.20
1.50	None	0.025	0.25
2.00	None	0.040	0.40
2.50	None	0.055	0.50
3.00	None	0.070	0.65
4.00	None	0.100	0.80
5.00	None	0.125	1.00
6.00	None	0.160	1.19
12.00	None	0.445	3.35
24.00	None	0.920	7.47
34.25	None	1.510	12.7
48.50	10X	0.255	20.3
60.50	10X	0.345	27.7
74.00	10X	0.500	40.5
86.50	10X	0.570	46.2
96.00	10X	0.670	54.4
108.00	10X	0.735	59.8
117.00	10X	0.785	63.9

DATA FROM HYDROYSIS STUDIES (CON'T)

Trial 12 - poly(EMCF) pellet

Time (hours)	Dilution	Optical Density	% 5-FU Released
0.25	None	0.000	0.00
0.50	None	0.000	0.00
0.75	None	0.010	0.10
1.00	None	0.020	0.25
1.50	None	0.030	0.35
2.00	None	0.050	0.55
2.50	None	0.055	0.60
3.00	None	0.070	0.70
4.00	None	0.080	0.80
5.00	None	0.090	0.90
6.00	None	0.095	0.92
14.00	None	0.110	0.97
24.00	None	0.160	1.45
34.25	None	0.235	2.20
48.50	None	0.355	3.40
60.50	None	0.440	4.30
74.00	None	0.570	5.60
86.50	None	0.635	6.20
96.50	10X	0.070	7.00
108.00	10X	0.085	8.50
120.00	10X	0.100	9.50
144.00	10X	0.125	10.5
166.50	10X	0.155	14.0
190.50	10X	0.190	17.6
216.40	10X	0.200	18.5
240.00	10X	0.230	21.6
264.00	10X	0.250	23.6
312.00	10X	0.270	25.5
338.00	10X	0.290	27.5
358.50	10X	0.300	28.6

DATA FROM HYDROLYSIS STUDIES (CON'T)

Trial 13 - 25% Methyl Acrylate

Time (hours)	Dilution	Optical Density	% 5-FU Released
0.25	None	0.025	0.25
0.50	None	0.055	0.54
0.75	None	0.060	0.55
1.00	None	0.070	0.59
1.50	None	0.085	0.64
2.00	None	0.115	0.89
3.00	None	0.135	1.07
4.00	None	0.155	1.25
5.00	None	0.180	1.47
6.00	None	0.200	1.66
12.00	None	0.375	3.21
18.00	None	0.615	5.37
24.00	None	0.895	7.86
30.00	None	1.190	10.5
36.00	None	1.530	13.6
49.00	10X	0.240	20.1
60.00	10X	0.290	24.6
72.00	10X	0.360	30.9
84.00	10X	0.430	37.1
97.00	10X	0.485	42.1
120.00	10X	0.565	49.2
144.00	10X	0.615	53.7
168.00	10X	0.640	55.9
192.00	10X	0.660	57.7
218.00	10X	0.670	58.6
240.00	10X	0.670	58.6
251.00	10X	0.670	58.6
264.00	10X	0.670	58.6
313.00	10X	0.670	58.6
336.00	10X	0.670	58.6
435.00	10X	0.670	58.6

DATA FROM HYDROLYSIS STUDIES (CON'T)

Trial 14 - 25% Methyl Acrylate

Time(hours)	Dilution	Optical Density	% 5-FU Released
0.33	None	0.020	0.21
0.67	None	0.035	0.35
1.00	None	0.050	0.49
1.50	None	0.060	0.55
2.50	None	0.095	0.71
3.50	None	0.120	0.94
4.50	None	0.135	1.07
5.50	None	0.150	1.20
11.00	None	0.275	2.33
17.00	None	0.485	4.20
23.00	None	0.770	6.70
29.00	None	1.010	8.90
35.00	None	1.310	11.6
48.00	10X	0.200	16.5
59.00	10X	0.270	22.8
71.00	10X	0.335	28.6
83.00	10X	0.395	34.0
96.00	10X	0.460	39.8
119.00	10X	0.550	47.9
143.00	10X	0.610	53.2
167.00	10X	0.640	55.9
191.00	10X	0.660	57.7
217.00	10X	0.670	58.6
239.00	10X	0.670	58.6
250.00	10X	0.670	58.6
263.00	10X	0.670	58.6
312.00	10X	0.670	58.6

DATA FROM HYDROLYSIS STUDIES (CON'T)

Trial 15 - 50% Methyl Acrylate

Time (hours)	Dilution	Optical Density	% 5-FU Released
0.25	None	0.000	0.00
0.50	None	0.010	0.17
0.75	None	0.010	0.17
1.00	None	0.010	0.17
1.50	None	0.015	0.25
2.00	None	0.035	0.54
2.50	None	0.060	0.92
3.00	None	0.090	1.04
4.00	None	0.170	2.16
5.00	None	0.250	3.26
6.00	None	0.310	4.10
12.00	None	0.565	7.64
18.00	None	0.685	9.30
24.00	None	0.775	10.6
30.00	None	0.840	11.4
36.00	None	0.905	12.4
42.00	None	0.970	13.3
48.00	None	1.015	13.9
60.00	None	1.115	15.3
72.00	None	1.190	16.3
96.00	None	1.370	18.8
120.00	None	1.530	21.1
144.00	None	1.720	23.8
172.00	None	1.970	27.1
192.00	10X	0.215	27.8
216.00	10X	0.225	29.1
240.00	10X	0.240	31.3
268.00	10X	0.280	36.8

DATA FROM HYDROLYSIS STUDIES (CON'T)

Trial 16 – 50% Methyl Acrylate

Time (hours)	Dilution	Optical Density	% 5-FU Released
0.33	None	0.010	0.17
0.67	None	0.015	0.25
2.50	None	0.025	0.39
3.50	None	0.135	1.66
4.50	None	0.225	2.91
13.00	None	0.560	7.58
19.00	None	0.640	8.69
26.00	None	0.710	9.72
34.00	None	0.770	10.5
45.00	None	0.870	11.9
60.00	None	0.940	12.9
84.00	None	1.100	15.1
108.00	None	1.250	17.2
132.00	None	1.405	19.3
156.00	None	1.570	21.6
198.00	10X	0.190	24.0
221.00	10X	0.200	25.7
240.00	10X	0.210	27.1
268.00	10X	0.220	28.4
291.00	10X	0.240	31.2
315.50	10X	0.260	34.0

DATA FROM HYDROLYSIS STUDIES (CON'T)

Trial 17 - 75% Methyl Acrylate

Time (hours)	Dilution	Optical Density	% 5-FU Released
0.33	None	0.000	0.00
0.67	None	0.000	0.00
1.00	None	0.000	0.00
1.50	None	0.010	0.36
2.50	None	0.025	0.86
4.50	None	0.030	1.00
5.50	None	0.050	1.70
6.50	None	0.060	2.10
15.00	None	0.125	3.50
21.00	None	0.135	3.80
28.00	None	0.160	4.60
36.00	None	0.195	5.70
47.00	None	0.235	6.90
60.00	None	0.280	8.35
84.00	None	0.345	10.4
108.00	None	0.370	11.2
132.00	None	0.415	12.6
156.00	None	0.435	13.2
198.00	None	0.460	14.0
221.00	None	0.495	15.1
240.00	None	0.590	18.1
268.50	None	0.700	21.6
291.00	None	0.800	24.9
315.50	None	0.905	28.1
340.50	None	1.015	31.6
354.50	None	1.075	33.4
386.00	None	1.220	37.9
390.50	None	1.370	42.7
408.00	None	1.450	45.4
435.00	None	1.610	50.4
603.00	10X	0.230	67.8

DATA FROM HYDROLYSIS STUDIES (CON'T)

Trial 18 - 75% Methyl Acrylate

Time (hours)	Dilution	Optical Density	% 5-FU Released
0.33	None	0.000	0.00
0.67	None	0.000	0.00
1,00	None	0.010	0.36
1.33	None	0.010	0.36
1.67	None	0.010	0.36
2.00	None	0.015	0.42
2.50	None	0.020	0.72
3.50	None	0.045	1.60
4.00	None	0.050	1.70
5.00	None	0.055	1.90
6.00	None	0.060	2.00
12.00	None	0.100	2.70
18.00	None	0.130	3.60
24.00	None	0.160	4.60
48.00	None	0.260	7.70
74.00	None	0.315	9.50
98.00	None	0.420	12.8
122.00	None	0.490	15.0
147.00	None	0.595	18.3
173.00	None	0.675	20.8
193.00	None	0.790	24.4
225.00	None	0.925	28.8

DATA FROM HYDROLYSIS STUDIES (CON'T)

Trial 19 - 25% Butyl Acrylate

Time (hours)	Dilution	Optical Density	% 5-FU Released
0.33	None	0.000	0.00
0.67	None	0.000	0.00
1.00	None	0.010	0.11
1.33	None	0.010	0.11
1.67	None	0.015	0.15
2.00	None	0.015	0.15
2.50	None	0.020	0.21
3.50	None	0.030	0.30
4.00	None	0.035	0.36
5.00	None	0.050	0.50
6.00	None	0.060	0.57
12.00	None	0.170	1.42
18.00	None	0.310	2.69
24.00	None	0.470	4.15
48.00	None	1.180	10.7
74.00	None	1.780	16.1
98.00	10X	0.220	18.7
122.00	10X	0.270	23.2
147.00	10X	0.305	26.5
173.00	10X	0.330	28.7
193.00	10X	0.380	33.3
225.00	10X	0.445	39.3

DATA FROM HYDROLYSIS STUDIES (CON'T)

Trial 20 - 25% Butyl Acyrlate

Time (hours)	Dilution	Optical Density	% 5-FU Released
0.33	None	0.000	0.00
0.67	None	0.000	0.00
1.00	None	0.000	0.00
1.50	None	0.005	0.06
2.50	None	0.010	0.11
4.50	None	0.020	0.21
5.50	None	0.025	0.25
6.50	None	0.030	0.30
15.00	None	0.130	1.05
21.00	None	0.230	1.96
28.00	None	0.370	3.24
36.00	None	0.550	4.89
47.00	None	0.780	7.01
60.00	None	1.030	9.28
84.00	None	1.460	13.2
108.00	None	2.800	16.3
132.00	10X	0.205	17.3
156.00	10X	0.210	17.8
198.00	10X	0.285	24.6
221.00	10X	0.330	28.7
240.00	10X	0.360	31.5
268.50	10X	0.400	35.2
291.00	10X	0.435	38.3
315.50	10X	0.465	41.1
340.50	10X	0.480	42.4
354.50	10X	0.495	43.8

DATA FROM HYDROLYSIS STUDIES (CON'T)

Trial 21 – 50% Butyl Acrylate

Time (hours)	Dilution	Optical Density	% 5-FU Released
0.25	None	0.000	0.00
0.50	None	0.005	0.10
0.75	None	0.010	0.20
1.00	None	0.015	0.20
1.50	None	0.030	0.50
2.00	None	0.045	0.70
3.00	None	0.070	0.90
4.00	None	0.090	1.00
5.00	None	0.125	1.50
6.00	None	0.150	1.80
12.00	None	0.265	3.40
18.00	None	0.370	4.80
24.00	None	0.445	5.80
30.00	None	0.470	6.10
36.00	None	0.510	6.60
49.00	None	0.575	7.50
60.00	None	0.615	8.10
72.00	None	0.655	8.60
84.00	None	0.685	9.00
97.00	None	0.725	9.60
120.00	None	0.765	10.0
144.00	None	0.820	10.8
168.00	None	0.870	11.5
192.00	None	0.895	11.8
218.00	None	0.925	12.1
240.00	None	0.965	12.7
251.00	None	1.030	13.6
264.00	None	1.040	13.7
313.00	None	1.060	14.0
337.00	None	1.090	14.4

DATA FROM HYDROLYSIS STUDIES (CON'T)

Trial 22 - 50% Butyl Acrylate

Time (hours)	Dilution	Optical Density	% 5-FU Released
0.33	None	0.010	0.20
0.67	None	0.015	0.20
1.00	None	0.025	0.40
1.50	None	0.065	0.90
2.50	None	0.110	1.30
3.50	None	0.145	1.70
4.50	None	0.170	2.10
5.50	None	0.190	2.40
11.00	None	0.290	3.70
17.00	None	0.375	4.80
23.00	None	0.425	5.50
29.00	None	0.485	6.30
35.00	None	0.495	6.40
48.00	None	0.565	7.40
59.00	None	0.600	7.90
71.00	None	0.645	8.50
83.00	None	0.680	8.90
96.00	None	0.715	9.40
119.00	None	0.760	10.0
143.00	None	0.805	10.6
167.00	None	0.865	11.4
191.00	None	0.890	11.8
217.00	None	0.920	12.2

DATA FROM HYDROLYSIS STUDIES (CON'T)

Trial 23 - 75% Butyl Acrylate

Time (hours)	Dilution	Optical Density	% 5-FU Released
0.33	None	0.35	0.28
0.67	None	0.35	0.28
1.00	None	0.55	0.44
1.33	None	0.55	0.44
1.67	None	0.55	0.44
2.00	None	0.55	0.44
2.50	None	0.55	0.44
3.00	None	0.060	0.46
3.50	None	0.070	0.49
4.50	None	0.080	0.51
12.50	None	0.110	0.70
30.00	None	0.130	0.85
36.50	None	0.145	0.96
51.00	None	0.160	1.07
60.50	None	0.165	1.11
84.50	None	0.170	1.14
92.50	None	0.185	1.25
101.50	None	0.200	1.37
114.00	None	0.210	1.46
133.50	None	0.220	1.51
146.50	None	0.230	1.59
156.50	None	0.235	1.63
171.00	None	0.245	1.69
178.00	None	0.255	1.77
190.00	None	0.275	1.92
219.00	None	0.295	2.07
240.00	None	0.310	2.17

DATA FROM HYDROLYSIS STUDIES (CON'T)

Trial 24 - 75% Butyl Acrylate

Time (hours)	Dilution	Optical Density	% 5-FU Released
0.25	None	0.000	0.00
0.50	None	0.000	0.00
0.75	None	0.005	0.04
1.00	None	0.005	0.04
1.50	None	0.010	0.09
2.00	None	0.010	0.09
2.50	None	0.010	0.09
3.00	None	0.015	0.13
4.00	None	0.020	0.17
5.00	None	0.020	0.17
6.00	None	0.025	0.20
12.00	None	0.055	0.44
18.00	None	0.080	0.51
24.00	None	0.095	0.59
30.00	None	0.105	0.66
36.00	None	0.115	0.74
42.00	None	0.125	0.81
48.00	None	0.135	0.88
60.00	None	0.145	0.96
72.00	None	0.155	1.03
96.00	None	0.185	1.25
120.00	None	0.210	1.44
144.00	None	0.225	1.54
172.00	None	0.255	1.77
192.00	None	0.270	1.88
216.00	10X	0.025	2.07
240.00	10X	0.027	2.22
268.00	10X	0.208	2.30
363.00	10X	0.045	3.68

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