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SOME PHYSICO-CHEMICAL FACTORS AFFECTING THE RELEASE OF SALICYLIC ACID AND RELATED DRUGS FROM OIL-IN-WATER EMULSIONS

by

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ABSTRACT

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The stability and release characteristics of some Miglyol-in-water emulsions were studied. The ternary phase diagrams of Miglyol, water and the selected anionic, cationic and non-ionic surfactants provided fundamental information about the stability of the emulsions produced.

The preliminary drug release experiments indicated that release from an emulsion was governed by the transfer of the drug from the oil phase, which was dependent on the type of the interfacial film. This was proved using different surfactants or surfactant mixtures to prepare the emulsions.

The effect of the apparent partition coefficient of the drug, which is a function of the oil/water phase volume ratio, ϕ, the micellar phase concentration and the pH of the external phase, on release was studied. The release was slower the greater the ϕ or, for the same ϕ, the higher the micellar phase concentration.

The effect of the partition coefficient on drug release was demonstrated, by incorporating different drugs in a model emulsion which showed that these two parameters are inversely related.

A trend towards a decreasing release rate from the oil with increasing viscosity was observed. However, the variations observed in the drug release from the emulsions could not only be attributed to the viscosity of the oil phase, but also to the changes in the interfacial film caused by the gelling agents.

The short and long term and the elevated stability tests proved that, except in the case of emulsions stabilized with Span 80 or Tween 20-Span 80 mixtures to produce low HLB values, the emulsions were stable. However, particle size distribution analysis determined by photosedimentometry has confirmed that microscopy was not a satisfactory method for accurate size distribution analysis and it provided only a gross visual check on the size distribution. This was due to the presence of a large number of globules in the submicrometer range.

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CONTENTS

CHAPTER 1

INTRODUCTION

1.1 Definition of emulsion

Although there are many definitions of an emulsion, the most comprehensive and generally accepted one is that given by Becher (1965):-

"An emulsion is a heterogeneous system, consisting of at least one immiscible liquid intimately dispersed in another in the form of droplets whose diameters, in general, exceed 0.1 μm. Such systems possess minimal stability, which may be accentuated by such additives as surface-active agents, finally divided solids, etc."

1.2 Pharmaceutical emulsions

Historically cosmetic emulsions represent the oldest examples of emulsions. Emollient and cosmetic creams have been known for literally thousands of years and the invention of cold cream is ascribed to Galen, the Greek physician in the second century. They have long been used to make mineral and fish oils more acceptable and nowadays emulsions find wide applications in various fields, such as foods, cosmetics, pharmaceuticals and wax polishes (Becher, 1965; Matsumato et al., 1978). Indeed, the Pharmaceutical Codex contains many formulae for creams which are used to render the topical applications of oily substances and medicaments both acceptable and possible.

Pharmaceutically, emulsions can be used for various purposes, e.g. as drug delivery systems to enhance or to

prolong drug absorption, or to deliver drugs to specific sites. Emulsified systems are also employed as diagnostic agents and for intravenous nutrition purposes. By conversion of a primary emulsion into a multiple emulsion its usefulness can be extended. The second emulsification of a water-in oil (w/o) primary emulsion giving a water-in oil-in water (w/o/w) system, reduces the overall viscosity of the formulation thus facilitating parenteral administration. The external phase of a w/o/w emulsion can also mask the taste of the oil for oral delivery or reduce the oiliness of the preparation for topical administration. A multiple emulsion of an oil-in water-in oil (o/w/o) type can be used as a vehicle for prolonged drug release based on the rationale that the drug must partition through an increased number of phases before it is released into the body fluids. The release could be further controlled by various formulation parameters, and both types of multiple emulsions have been reported to be very useful by many researchers.

Numerous studies have indicated that emulsions can be used to facilitate the absorption of drugs particularly those of low water solubility. This effect is probably due to the large surface area of the oil droplets that are exposed to the gastro-intestinal fluids. Lewis, Cohlar and Messina (1950) found that vitamin A absorption was increased when given in an emulsion. Feinstone, Wolff and Williams (1940), Svenson et al. (1956) and Daeschner et al. (1957) studied the oral absorption of sulphonamides and concluded that absorption from a liquid emulsion was more rapid and more complete than from an aqueous suspension.

Wagner, Gerard and Kaiser (1966) compared the absorption of indoxole, an oil soluble anti-inflammatory agent, from an o/w emulsion with a capsule formulation and an aqueous suspension and found that the order of the response was emulsion, soft elastic capsule, aqueous suspension and powder in capsule. Enhanced bioavailability of griseofulvin, a relatively water-insoluble antibiotic, from an emulsion has also been observed (Carrigan and Bates, 1973; Bates et al., 1975). Better and more complete absorption of vitamin A acetate and phenylbutazone (Ogata et al., 1975), urogastrone (Hori et al., 1977), vitamin E (Newmark et al., 1975), phenytoin (Chakrabarti, 1978; Shinkuma, 1981), corticosteroids from lipid emulsions have also been reported (Mizushima, Hamano and Yokoyama, 1982). A list of publications on enhanced release from emulsions is given in Table 1.1.

Emulsions can be used as sustained or prolonged release drug delivery systems (Table 1.2). Jeppsson (1972a; 1972b) has reported a quick onset of action and prolonged anaesthetic activity, when lipid-soluble barbiturates were administered in emulsions rather than aqueous and oily solutions of the drugs. Also administration of vasoactive drugs, namely cyclandelate and nitroglycerin, in soya bean emulsions suggested that emulsions could be a suitable vehicle for intravascular administration of lipid soluble drugs (Jeppsson and Ljungberg, 1973). More recently, the use of multiple emulsions as parenterally administered drug delivery systems for prolonging the effect of naltrexone, a narcotic antagonist, and thymol have been reported (Frank, Brodin and Kavaliunas, 1976; Brodin and Frank, 1978).

Table 1.1. Enhanced release from emulsified systems.

Type	Drug	Route	Remarks	Reference
o/w	Vitamin A	Oral	Increased and more complete absorption.	Lewis, Cohlan and Messina, 1950.
o/w	Sulphonamides	Oral	More rapid and more complete absorption than the aqueous suspension.	Feinstone, Wolff and Williams, 1940; Svenson et al., 1956; Daeschner et al., 1957.
o/w	Indoxole	Oral	The order of response was: emulsion, soft elastic capsule, aqueous suspension, powder in capsule.	Wagner, Gerard and Kaiser, 1966.
o/w	Griseofulvin	Oral	Rapid, uniform and complete absorption from the emulsion than the aqueous and the oil solution.	Carrigan and Bates, 1973.
o/w	Griseofulvin	Oral	Absorption was better than aqueous solution and two different commercial tablet form.	Bates and Sequeira , 1975.

Table 1.1 Continued

Type	Drug	Route	Remarks	Reference
o/w	Vitamin A acetate and butazone	Intestinal absorption in situ	Better and complete absorption.	Ogata et al., 1975.
o/w	Vitamin E Sulfisoxazole, Dicumarol and Griseofulvin	I.V., I.M. oral	Rapid and complete absorption. Digestible lipids increased the bioavailability.	Newmark et al., 1975; Bloedow and Hayton, 1976.
o/w	Urogastrone	I.V., I.P. I.J.	Better and complete absorption.	Hori et al., 1977.
o/w	Phenytoin	Oral	Better absorption from emulsion than the oily suspension and aqueous solution.	Chakrobarti and Belpaire, 1978.
o/w	Phenytoin	Oral	The ratio of oil to water was an important factor on the absorption rates of the drug.	Shinkuma et al., 1981.
o/w	Corticosteroids	I.V.	Enhanced bioavailability and stronger anti-inflammatory activity.	Mizushima, Hamano and Yokoyama, 1982.

Table 1.2. Prolonged release from emulsified systems.

Type	Drug	Route	Remarks	Reference
o/w	Thiopental, hexabarbital, secobarbital, cyclobarbital and pentobarbital	I.V.	In all cases emulsions gave a prolonged duration of sleep. The onset of action was immediate with ultra-short acting barbiturates, but a slight prolongation was noticed with short acting barbiturates.	Jeppsson, 1972a.
o/w	Thiopental, secobarbital	I.P. SC.	A depot effect was observed with the emulsion form.	Jeppsson, 1972b.
o/w	Cyclandelate and nitroglycerin	I.A.	Emulsion may be a suitable vehicle for intravascular administration of lipid soluble vasoactive drugs.	Jeppsson and Ljunberg, 1973.
o/w/o	Naltrexone HCl	In vitro	A three-fold prolongation of release of drug from the emulsion compared with that of oily suspension.	Frank, Brodin and Kavaliunas, 1976.

Table 1.2 Continued

Type	Drug	Route	Remarks	Reference
w/o/w and o/w/o	Naltrexone HCl	In vitro	70% reduction in effective diffusion coefficient was obtained by addition of electrolytes to the internal phase.	Brodin, Kavaliunas, and Frank, 1978.
o/w/o	Naltrexone HCl and thymol	In vitro	Transfer across the inner o/w interface was rate limiting for naltrexone, however external oil phase was rate limiting for thymol.	Brodin and Frank, 1978.

The properties of the surfactant at the inner w/o interface were affected by the presence of sodium chloride or sorbitol in the external aqueous phase, and surfactants become more effective as a mechanical barrier for the transfer of the drugs by forming liquid crystalline phase at the interface (Brodin, Kavaliunas and Frank, 1978; Frank, Brodin and Kavaliunas, 1976) (Table 1.2).

Freund et al. (1944) demonstrated that enhanced and prolonged antibody titres of diphtheria toxoid were obtained when the emulsified vaccines were administered. By emulsifying the aqueous solution in mineral oil, poor antigenic activity of single dose parenteral solutions were considerably improved. Since this original discovery, many other emulsion vaccines have been developed (Salk et al., 1953; Freund, 1956; Berlin, 1960; Davenport, 1961; Lazarus et al., 1967). Because w/o emulsions have high viscosity and are difficult to inject, Herbert (1965) suggested a second emulsification of the mineral oil emulsions which also produced a better and sustained level of response. Many vaccines have been formulated as multiple emulsions since then and some are summarized in Table 1.3.

Emulsions can be used to facilitate the gastro-intestinal absorption of usually non-absorbable biopolymers or to protect a drug from rapid degradation. Multiple emulsions with their lower viscosity and extra partitioning step would appear to be potentially useful for such purposes. Engel, Riggi and Fahrenbach (1968) have first shown a significant drop in glucose levels when insulin is included in a w/o/w system administered by intraduodenal injection

Table 1.3. Emulsions as adjuvants.

Type	Vaccine	Route	Remarks	Reference
w/o	Diphtheria toxoid and typhoid bacilli	S.C.	Paraffin oil enhanced and sustained the formation of antibodies, peanut oil had almost no effect.	Freund and Bonanto, 1944.
w/o	Influenza virus	S.C.	Antibody levels were higher and higher levels were maintained longer than that of the aqueous solutions of the virus.	Salk et al., 1953.
			A review on the subject.	Freund, 1956.
w/o	Influenza virus	S.C.	Stability and the viscosity of the emulsion affected the response.	Berlin, 1960.
w/o	Influenza virus	S.C.	A discussion on the use of emulsion adjuvants in prophylactic immunization and pre-seasonal treatment of allergy was given together with some results.	Davenport, 1961.
			A review on immunization by emulsion adjuvants.	Lazarus and Lachman, 1967.

Table 1.3 Continued

Type	Vaccine	Route	Remarks	Reference
w/o/w	Ovalbumin	S.C.	The multiple emulsion has a low viscosity, produces diffuse depots.	Herbert, 1965.
w/o/w, w/o	Influenza virus	S.C.	The multiple emulsion gave a higher antibody titre than w/o emulsion and aqueous solution.	Taylor et al., 1969.
w/o/w	Human serum albumine	S.C.	Stimulation of antibody response was high.	O'Neill, Henderson and White, 1973.
w/o/w	Bovine serum albumin	S.C.	More persistent response was obtained, when the antigen administered via w/o/w emulsion.	Aitken, 1973.
w/o/w	Antigen for haemorrhagic septicemia	S.C.	Multiple emulsion was found equally immunogenic as an oil adjuvant and easier to administer.	Mittal et al., 1977.

to rats and gerbils. However, in this study, the enteral absorption of insulin emulsion was evaluated by the indirect measurement of the hypoglycaemic response. To obtain additional information on the enteral absorption of insulin Shichiri and co-workers (1974; 1975; 1976; 1978) have extended this approach to the direct measurement of plasma concentrations of insulin. These extensive studies are summarized in Table 1.4.

As a rule, water soluble compounds of molecular weight greater than 200, penetrate the mucosal cell only with considerable difficulty, and ionized compounds are generally absorbed at a rate much lower than that of neutral molecules. It has long been recognized that the gastro-intestinal tract is normally impermeable to aqueous solutions of Heparin which has a molecular weight of 14,000, but Engel and Fahrenbach (1968) and Engel and Riggi (1969) have reported that absorption of heparin can occur when the polysaccaride is presented to the intestinal mucosa of rats and gerbils in the form of an o/w emulsion and that vegetable oils were more effective than mineral oils.

In recent years there have been a number of reports on the use of emulsions as drug delivery systems to the target sites, especially in cancer chemotherapy, as a means of enhancing the transport of anticancer agents in the lymphatic system. In order to prevent metastasis along the lymphatic pathways, it is essential to create a selectively high concentration of the drug and multiple emulsion systems have been reported to satisfy these conditions. Also a novel emulsion form consisting of microspheres in oil, has been

Table 1.4. Emulsion vehicles to protect the drugs from degradation.

Type	Drug	Route	Remarks	Reference
w/o/w	Insulin	I.D.	A significant drop in glucose levels.	Engel, Riggi and Fahrenbach, 1968.
w/o/w	Insulin	I.J.	A significant drop in blood glucose levels and in excreted glucose when compared to insulin solution.	Shichiri et al., 1974.
w/o/w	Insulin	I.J.	Administration of multiple emulsion 3 times daily, maintained the decrease in blood and excreted glucose levels but total absorption of insulin was low.	Shichiri et al., 1975.
w/o/w	Insulin	Oral	Total absorption and the effect of insulin was better as emulsion than that of aqueous solution.	Shichiri et al., 1976.
Micellar Insulin emulsion		Oral	Micellar form of insulin was twice as effective as the previous w/o/w emulsions.	Shichiri et al., 1978.

Table 1.4 Continued

Type	Drug	Route	Remarks	Reference
o/w o/w	Heparin Heparin	I.D.	Absorption can occur when Heparin is administered in an emulsion and that vegetable oils were more effective than mineral oils.	Engel and Fahrenbach, 1968. Engel and Riggi, 1969.

tested and has proved to be a better system than w/o emulsions. Furthermore, it satisfied many criteria of an ideal drug delivery system to deliver anticancer drugs into specific target sites (Hashida et al., 1977 a, b and c; 1979; 1980 a and b). In addition, o/w emulsions have been reported as vehicles of antitumour vaccines as summarized in Table 1.5.

Another field in which emulsions could be useful is the use of fluorinated hydrocarbon emulsions as blood cell substitutes. Blood presents numerous and difficult problems when complete replacement with artificial materials is attempted. Geyer (1974) summarized the basic requirements for a blood substitute and the difficulties of preparing one. He also summarized some of his own studies on the total replacement of blood (cells and plasma) of living rats with a fluorocarbon emulsion (Geyer, 1974) reporting that such animals survived and also regenerated new blood cells and plasma proteins, subsequent growth and development being normal. Although an atmosphere of 90% to 100% oxygen was provided during these experiments, this was the first successful attempt to exchange the whole blood. Earlier, Boerema et al. (1960) had exchanged the blood of pigs with a Dextran-saline solution, but although the animals were given back whole blood after about one hour, all animals developed lung edema and half of them died. Clark and Gollan (1966) found the inert fluorocarbon liquid to have about 50 times as large a capacity as that of water for dissolving oxygen while having an ability similar to haemoglobin to transport oxygen to tissue in vivo. Since

Table 1.5. Emulsions as drug delivery systems to deliver drugs into specific sites.

Type	Drug	Route	Remarks	Reference
w/o/w	Methotrexate	I.P.	3 mg / kg drug administered in emulsion gave a longer survival time than 80 mg / kg of aqueous solution.	Elson et al., 1970.
w/o/w	Methotrexate, cytosine arabinoside and vinblastine sulphate	I.P.	Smaller doses of drugs administered in emulsions gave similar responses as aqueous solutions of larger doses.	Benoy et al., 1972.
w/o and o/w	Mitomycin and bleomycin	I.M. and I.P.	w/o emulsion was the most effective, but both emulsion formulations were better than aqueous solutions.	Nakamoto et al., 1975 a and b.
w/o and w/O-G	Iodohippuric acid and tripalmitin	I.M. and regional	Transfer of the drugs was enhanced in the following order : oil, o/w, w/o and w/O-G (gelatin microsphere/oil) emulsion.	Hashida et al., 1977 a and b.

Table 1.5 Continued

Type	Drug	Route	Remarks	Reference
w/o, s/o	S-Fluorouracil	I.G., I.M. and I.V.	w/o and s/o (microsphere-in oil) emulsions satisfy many criteria of an ideal drug delivery system.	Hashida, Muranishi and Sezaki, 1977c.
w/o, s/o	Bleomycin	Regional injection	Superior effect of s/o emulsion in surgical adjuvant chemotherapy was reported.	Hashida et al., 1979.
w/o, s/o	S-Fluorouracil	In vitro	Stability and other physical properties of s/o emulsion compared with the properties of w/o, together with drug release.	Hashida et al., 1980a.
w/o, s/o	Tripalmitin	I.M.	s/o was the best, w/o emulsion was the next most effective emulsion compared with oil solution. Also effect of injection volume and massage of the injection site were reported.	Hashida et al., 1980b.
o/w	Methyl CCNU	I.V.	Drug was administered in Intralipid (Vitrum, Stockholm, Sweden) and no side effect was observed.	Fortner et al., 1975.

Table 1.5 Continued

Type	Drug	Route	Remarks	Reference
w/o and w/o/w	Bleomycin and Mitomycin	Into tumoral, I.V.	Higher levels of drugs were found in the tumour when administered in an emulsion than an aqueous solution.	Takahashi et al., 1976.
o/w	Cord factor	Intralesional inoculation	Emulsion can be used successfully in antitumour immunotherapy. Antitumour vaccines were more effective in mineral oil emulsions rather than vegetable oil emulsions, only squalane and squalene were effective substitutes for mineral oil.	Yarkoni, Meltzer and Rapp, 1977. McLaughlin et al., 1978. Pimm et al., 1979. Yarkoni and Rapp, 1979. Pimm, Baldwin and Lederer, 1980.

then many workers have reported the formulations of blood substitutes (Table 1.6). Although fluorocarbons have a high capacity for dissolving gases, they must be emulsified in electrolyte solutions to give the same pH and osmolality as blood and thus oxygen carrying capacity is lowered (Sharts et al., 1978; Endrich et al., 1980). Therefore higher concentrations of fluorocarbon in the emulsion would be needed to provide an oxygen carrying capacity comparable to whole blood, and this could exceed the tolerable fluorocarbon concentration. Fluorocarbon emulsions also can cause deterioration of microhemodynamic function and damage to endothelial and blood cells (Endrich et al., 1980). Another disadvantage of fluorocarbon emulsions is the accumulation in the organs and tissues (Federov et al., 1980) and toxic reactions due to the larger particle sizes of the globules which should be 0.3 μm or less (Fujita, Sumaya and Yokoyama, 1971).

Despite all the effort expended on this topic, the sole commercially available product is for animal use only (Fluosol). If the difficulties and disadvantages were overcome and such a product became available for human use, the advantages over human replacement blood would be immense: good shelf life, no blood group problems, ready accessibility in large quantities, no risk of hepatitis and easy to use in emergencies. In fact, all these advantages were demonstrated in an emergency operation when Fluosol-DA 20% (Green Cross Corporation, Osaka, Japan) was used successfully for the first time (Honda et al., 1980).

Table 1.6. Perfluorocarbon emulsions as blood substitutes.

Fluorocarbon	Remarks	Reference
FX-80	Reviewed the basic requirements for a blood substitute, and reported the whole exchange of blood with an emulsion in rats.	Geyer, 1974.
Dextrane-saline	Unsuccessful attempt of exchanging the blood of pigs.	Boerema et al., 1960.
FC-80	The oxygen dissolving capacity of FC-80 was reported to be 50 times as large as that of water.	Clark and Gollan, 1966.
FX-80	Emulsion of FX-80 gave good electro-potential data when perfused isolated rat brain.	Sloviter and Kamimato, 1967.
FX-80, FC-43	Toxicity of fluorocarbon emulsions was related to the particle size of the emulsion; the larger the particles the more toxicity and vice versa, and should be 0.3 μm or less.	Clark et al., 1970. Sloviter, Yamada, Ogoshi, 1970. Fujita, Sumaya and Yokoyama, 1971.
FC-47, $C_8F_{17}Br$	Oxygen carrying capacity of the fluorocarbons were lowered by emulsification, and it was only about 4 times higher than that of water.	Sharts et al., 1978. Endrich et al., 1980.

Table 1.6 Continued

Fluorocarbon	Remarks	Reference
Perfluorotributylamine	PFTBA was reported to be a good solvent for oxygen, although there was the disadvantage of accumulation of PFTBA in the tissues.	Federov et al., 1980.
Perfluorodecalin	Low toxicity and high ability to transport oxygen, PFD emulsion could be a suitable medium as an artificial blood.	Chaplygina et al., 1981.
Perfluorodecalin and perfluorotributylamine (Fluosal-DA 20%)	The first therapeutic use of oxygen-transporting blood substitute in an emergency operation.	Honda et al., 1980.

Emulsified systems are also employed as diagnostic agents in the form of injectable radiopaques which can be divided into water and oil-soluble types. Due to their extremely rapid absorption, the water-soluble radiopaques are far from being completely satisfactory and repeat exposures are virtually impossible. In order to obtain opacity, solution concentrations over 20% must be used, but such a concentration is strongly hypertonic and irritating to the tissues, causing severe discomfort. In comparison, non-irritating oil-soluble ones are slowly absorbed and eliminated, but they may form granulomas and emboli if injected into the venous system (Ginsburg and Skorneck, 1955; Davies, 1956). A possible solution to this problem might be the utilization of an emulsified form of the oils and investigators have attempted this approach by considering the formulation of diagnostic vehicles. Emulsions of Iophendylate have been prepared and studied (Chalecke et al., 1947; Jaeger, 1950). Since this time, many emulsion formulations have been tested (Table 1.7), but despite good opacity, they were completely miscible with body fluids producing an even coating of body membranes and their elimination was more rapid than that of the non-emulsified oil. Even so, toxicity, probably due to the small particle size, was the main problem (Chalecke et al., 1947; Jaeger, 1950; Kunz, Lewis and Sperandio, 1965). Long et al. (1972 a and b) attempted to use brominated perfluorocarbon compounds choosing perfluorooctyl bromide as a promising new radioopaque, while Arambulo et al. (1974-1975) have carried out extensive studies on it. Grimes et al. (1979)

Table 1.7. Radiopaque emulsions.

Radiopaque	Remarks	Reference
	Oil soluble radiopaques have been criticised for water immiscibility, slow absorption, production of granulomas etc.	Ginsburg and Skorneck, 1955. Davies, 1956.
Iodophendylate	Toxicity of the material was 10 times increased by emulsification. Probably due to the small particle size of globules.	Chalecke et al., 1947.
Iodochlorol		Jaeger, 1950.
Iodized oils	Although elimination of the emulsified media was more rapid than that of iol, toxicity increases upon emulsification.	Kunz, Lewis and Sperandio, 1965.
Perfluorooctyl bromide	Brominated perfluoro compound proved to be more promising and the emulsions were quite acceptable.	Long et al., 1972 a and b. Arambulo et al., 1974-1975.
Ethiodized oils	Size of the oil globules is of primary importance in the opacification of the specific tissues.	Grimes et al., 1979.

suggested that the size of the oil globules is of primary importance in the opacification of the specific tissues.

Total parenteral nutrition has been one of the most important advances in acute patient care during the past decade. It is a means of providing intravenous nutrition to patients who are unable to absorb nutrients via the gastrointestinal tract. During recent years, intravenous fat emulsions have gained in popularity as a caloric source, viz. a 10% fat emulsion has 1.1 cal/ml. In America emulsions containing 10% fat have been used while most European countries have used double that concentration, Glycerol, a water soluble substance, being added to make these fat emulsions isotonic.

Fat was first administered parenterally in 1869 (Wentzel and Perco, 1869). After comprehensive animal experiments these workers gave a subcuteneous injection of fat to a patient in an emaciated condition. Later, Hodder (1873) used intravenous infusion of milk as a treatment for cholera. The first systemic attempts to administer artificial fat emulsions to man were carried out in Japan between 1920 and 1930. Nowadays, there are many commercial emulsions available such as Intralipid, Lipumol, Infonutrol, Lipofundin and Lipiphysen which contain either cottonseed oil or soybean oil. Acceptable doses and, most importantly, elimination of fat emulsion from tissues has been under investigation (Zenk, 1981; Davis et al., 1980; D'amico et al., 1980). Hallberg et al. (1967) have summarized early findings on fat emulsions for complete intravenous nutrition. They also compared soybean and cottonseed oil emulsions as

intravenous emulsions. Meng (1972) reviewed the use of fat emulsions in parenteral nutrition stating that, although IV administration of fat emulsions was useful to give energy and to meet the requirement of essential fatty acids, there could be some long term effects that were not well understood, especially with regard to fat transport, metabolism and elimination. In a recent review article, many of these problems of fat emulsions have been discussed and a number of publications were given (Pelham, 1981).

1.3 Advantages and disadvantages of emulsions as drug delivery systems

Although emulsions have a potential use in drug delivery, their advantages are counterbalanced by an increased complexity of the dosage form and the problems of optimal formulation and acceptable stability. Emulsions being dispersed systems, have large surface areas with correspondingly large surface energies and are, therefore, thermodynamically unstable but the time taken for them to break may be sufficiently long for pharmaceutical purposes. The composition of an emulsion usually gives little indication of stability, and this is further complicated by the presence of drug molecules which will affect the emulsion stability either alone or by interacting with the oil or emulsifier. However changes in stability are very important since these will affect drug release or vice versa. Other problems associated with the oral administration of emulsions are the low pH and high ionic strength of the stomach environment and the consequent effect on emulsion stability. The relatively high ionic strength of plasma can also cause

instability of an emulsion administered intravenously. The chemical stability of a drug can be tested by storage under set conditions, but there is no simple equivalent test for emulsions, and the lack of an accelerated stability test restricts their development. The only reliable test is storage for the required period, but this is, of course, expensive and time-consuming.

Despite these drawbacks, emulsions have many advantages over more widely used dosage forms. By administration of a drug in an emulsion, it is possible to achieve enhanced absorption (Table 1.1) and prolonged release (Tables 1.2 and 1.3), or to achieve absorption of drugs which are not normally absorbed (Table 1.4). Emulsions are also used for application of oil soluble radiopaques (Table 1.7), or as blood substitutes (Table 1.6) and for intravenous nutrition. Another useful application of emulsified systems is to deliver anticancer drugs to the target sites (Table 1.5). Therefore, if the disadvantages were overcome, emulsions would be very useful as drug delivery systems.

1.4 Emulsion stability

1.4.1 Theories of emulsion stability

As stated earlier, emulsions are never completely stable in the absolute sense, because of the large interface and surface energy, therefore globules tend to join together to reduce the interfacial area. Since coalescence of drops is a thermodynamically spontaneous process, the reverse process requires work and consequently does not occur spontaneously. In order to reduce the work required, surface active agents are used to lower the interfacial

tension although this is not the only effect of emulsifying agents. Non-surface active agents, such as gums, fine solids etc. also could be used. In general, emulsifying agents are added to produce an interfacial film surrounding the droplets (Gopal, 1968).

Emulsion instability may be initiated by aggregation of the droplets of the discontinuous phase which may remain dispersed or flocculate together, but eventually flotation or sedimentation, depending upon the density of the oil phase, would result in a clearance of the continuous phase. This process is referred to as "creaming" and is reversible but when aggregates coalesce a well-defined layer of oil may separate irreversibly. The third process is molecular diffusion which is a slow and irreversible process and also leads to an increase in particle size by the diffusion of disperse phase from the smaller to the larger drops. Finally, the fourth process, "flocculation", is a reversible aggregation of drops into clumps, followed by a rapid creaming.

1.4.1.1 Adsorption theories of emulsion stability

Bancroft (1913 and 1915) was the first to recognize that the emulsifying agent is concentrated in the interface to form an interfacial film which has a stabilizing effect. He also pointed out that the phase in which the emulsifier is more soluble will be the external one. Later, the theory was put more elaborately by Bancroft and Tucker (1927) stating that an interfacial film requires two interfacial tensions and the film would curve in the direction of the higher interfacial tension. Harkins, Davies and Clark (1917)

also reported that when surfactants are adsorbed at the interface, the molecules are oriented such that the hydrophilic portion favours the aqueous phase and hydrophobic hydrocarbon chain favours the oil. The formation of this ordered monomolecular film results in a marked decrease in surface energy at the interface and this leads to stabilization of the emulsion. The type of the emulsion depends upon the relative dimensions of the hydrophilic and hydrophobic portions of the molecule. Molecules tend to fit themselves to the curvature of the droplet, thus behaving like a wedge. As a result, emulsifiers having large hydrophobic portions, such as bivalent metal soaps, favour the formation of w/o emulsions. On the other hand, monovalent metal soaps with a relatively small hydrophobe, tend to form o/w emulsions (Harkins et al., 1917). However, exceptions to this theory are known such as silver soaps which should, by the "oriented wedge" concept, yield o/w emulsions but actually stabilize the opposite type. Other exceptions to this rule have been reported by Wellman and Tartar (1930). Therefore, the simple solubility rule of Bancroft (1913) has more validity than the oriented wedge theory which has, on the other hand, a certain conceptual value to explain the inversion of soap stabilized emulsions on the addition of salts of multivalent metals.

Schulman and co-workers (Schulman and Stenhagen, 1938; Schulman and Cockbain, 1939 and 1940; Schulman and Rideal, 1937) related the properties of monomolecular films formed on the droplets to emulsion stability. They observed that strong complexes could be formed in the interface between

water soluble and water insoluble materials such as between soaps and long chain alcohols, by penetration of one into the film formed by the other. The formation of such a closely packed liquid-condensed film results in better stability of the emulsion, because the liquid property enables the film to be easily reformed after distortion and the complex formation allows the incorporation of more charged material into the interface (Alexander and Schulman, 1940; Schulman and Cockbain, 1940). It was also found that the stability is best when the droplets are no larger than 3 μ in diameter and even smaller diameters are preferable. The validity of this concept of stabilization was questioned by Dickinson and Iball (1948) who tried to emulsify mineral oil and cyclohexane in water by sodium laurate as the o/w emulsifier and monoolein as the w/o emulsifier. Together these two emulsifiers would give rise to complex formation, and separately form opposite emulsion types. However, addition of monooleate to the poor cyclohexane emulsion stabilized by sodium laurate, resulted in inversion of the o/w emulsion to a reasonably stable w/o emulsion. Also, the emulsion type reversed at 50% mineral oil when the mixtures of the two oils and water emulsified with two of the emulsifiers, due to the increased viscosity of the oil phase and its effect on the emulsification process. The rate and means of mixing, and the phase volume ratios also affect the emulsion type. Therefore, although the physical structure of the interfacial film is important, it is not the only governing factor.

1.4.1.2 Interfacial film and interfacial viscosity

Although Blakey and Lawrence (1954) noted that high interfacial viscosity does not occur in many stable systems and in general plays no part in the stabilization of emulsions, especially o/w, Sherman (1953) and Becher (1962) have shown that a highly viscous, even rigid, interfacial film forms in many emulsion systems as a mechanical barrier to the coalescence of the liquid droplets. Cockbain and McRoberts (1953) stated that the coalescence of single drops at the oil/water interface occurs in two stages similar to the breakdown of foams. These are,

(1) drainage of continuous phase and interfacial film from between the drop and the bulk disperse phase, and

(2) rupture of the adsorbed film.

Gillespie and Rideal (1956) suggested that rupture may occur before complete drainage, so that the film thickness may not always be the same at rupture. Kitchener and Musselwhite (1968) stated that a low interfacial tension leads to slower drainage of the interfacial film from between coalescing droplets. Serrallach and Jones (1931) and Serrallach, Jones and Owen (1933) have called the interfacial films "tough skins" and an example of this was found also by Shotton (1955) who showed that, after a monolayer had formed, further addition of acacia to the system caused the formation of a multilayer which had gel-like properties. This multilayer film could not be removed by dilution of the continuous phase (Shotton, 1955). Therefore, interfacial adsorption of acacia did not comply with the Gibbs adsorption isotherm.

Some surfactants can also stabilize emulsions by the steric effect (Elworthy and Florence, 1969a,b; Napper and Netschey, 1971; Napper, 1977). Napper et al. (1971) showed that Pluronic F-68, polyoxypropylene-polyoxyethylene ether, stabilized dispersions as a result of the polyoxyethylene chains extending into the medium from the surface of the dispersed particles. The thermodynamic barrier to the interpenetration of the chains prevents the approach of particles to each other and other non-ionic surfactants with their polyoxyethylene chains would be expected to behave similarly. Detailed ternary phase diagrams showed that good stability in an emulsion is associated with liquid crystalline layers around the drops (Friberg and Mandell, 1970a; Friberg, 1971; Friberg, 1979). A number of other observations have showed the rheological properties of the absorbed mixed emulsifier film, such as viscoelasticity, around the drops to be important and affect the stability of emulsions (Boyd, Parkinson and Sherman, 1972; Boyd, Krog and Sherman, 1976; Sherman and Benton, 1980; Kirikou and Sherman, 1979; Oosterbroek et al., 1981 a and b).

Ever since Griffin (1949) defined the hydrophilic lipophilic balance, HLB, as the ratio between the influence of the hydrophilic and lipophilic groups of an emulsifier, attempts have been made to relate this to emulsion stability. Although HLB does not indicate the overall efficiency of the emulsifier it is predictive with regard to the type of emulsion that can be expected (Griffin, 1949). Further correlation was found between the emulsion stability and the spreading coefficient and HLB (Becher, 1960) and the

temperature (Shinoda, 1967; Saito and Shinoda, 1970; Shinoda and Sagitani, 1978). Temperature affects the dissolution state of non-ionic surfactants and the hydrophilic-lipophilic property of a surfactant balances for a given oil-water system at a temperature which is called the phase inversion temperature (PIT). The relationship between the PIT, HLB and emulsion stability has been given in a number of publications (Sunderland and Enever, 1972; Enever, 1976; Shinoda, 1967; Saito et al., 1970; Shinoda et al., 1978; Takamura et al., 1979; Marszall, 1975; Little, 1978; Hayes et al., 1979) and the concept has found a practical application in emulsion technology. The inversion of an emulsion will alter the thermal properties, therefore, any technique which provides information about any of these thermal properties will be suitable for determining PIT. Sherman and co-workers adopted differential thermal analysis (DTA) to obtain more accurate results more quickly than the previous visual technique (Matsumoto and Sherman, 1970), and this technique has been used also as an accelerated stability test. Matsumoto and Sherman (1970) showed that phase inversion was an endothermic process and the PIT changed whenever structure and orientation of the surfactant molecules at the interface changed. The PIT was much lower for w/o emulsions than for o/w emulsions and at higher temperatures the w/o emulsion did not invert but broke due to the insolubility of hydrophobic emulsifier in water.

1.4.1.3 Electrical theories of emulsion stability

In the previous section, emulsion stability has been reviewed on the basis of the geometry and physical properties of the interfacial layer. It is necessary to consider the possible stabilizing effects of the charge which arises from the ionization of the emulsifying agent molecules adsorbed on the droplets. For example, if an emulsion is stabilized by a soap, the oil droplets will be effectively surrounded with a coating of negatively charged carboxyl ions and this will lead to a greater concentration of cations in close proximity to the drops. In emulsions stabilized by cationic agents, a positive charge is obtained but, on the other hand, ionization is not the cause of the charge in emulsions stabilized by non-ionic emulsifiers. Here, frictional contact between the droplets and the dispersion medium generates the charge. As Coehn (1898) has stated, a substance having a high permittivity is positively charged when in contact with another substance having a lower permittivity. Therefore, the droplets of o/w emulsion will be negatively charged, whereas w/o emulsion droplets will have a positive charge. Due to the mutual repulsion of the similarly charged droplets, stability of the emulsion improves.

In order to explain the existence of a surface charge, Helmholtz (1879) introduced the concept of the "electrical double layer" which stated that the charge was due to an unequal distribution of ions at the particle-water interface and added that ions of one charge were closely bound to the particle, whereas ions of the opposite charge would line up

parallel to them forming a double layer of charges. Gouy (1909) has pointed out that due to the mobility of the ions a double layer as conceived by Helmholtz (1879) could not be formed but would be diffuse and electrical density would decrease exponentially. In 1924, Stern proposed another theory in which the diffuse layer is in two parts: one, which is a single ion in thickness and remains fixed to the surface giving a sharp potential drop (Helmholtz layer) and the second extends into the dispersing phase and is diffuse with an exponential fall in potential into the bulk of the liquid.

The effect of the potential of the double layer upon the repulsion energy is influenced by the thickness. Increasing the ionic strength of the continuous phase leads to a reduction in double-layer thickness which in turn lowers the potential energy of repulsion and alters the stability of an emulsion.

1.4.2 Methods of assessing emulsion stability

1.4.2.1 Phase separation

As an emulsion deteriorates, it can undergo creaming, flocculation, coalescence and finally break. Some workers (Griffin and Behrens, 1952, 1954 ; Appino, Christian and Banker, 1962; Zatz, 1979; Reddy and Fogler, 1981 a and b) have suggested that measurement of the extent of creaming can be used to assess emulsion stability. Density differences between the particles and the dispersion medium are the cause of creaming with the larger particles creaming at a faster rate than the smaller ones, but the extent of

creaming does not give a satisfactory evaluation of emulsion stability since the globules undergo a substantial coalescence. However, creaming and phase separation measurements do give an indication only about grossly unstable emulsions.

1.4.2.2 Particle size analysis

In studies of the stability of emulsions, the change in the particle size distribution with time is often the most important parameter.

The droplet size analysis of emulsions has been studied by Groves (1966) who also reviewed the available methods (Groves et al., 1968). Many workers have studied the particle size distribution of emulsions by different methods and reported that no one method was able to cover the wide range of diameters, especially the sub-micron range, in emulsified systems.

Perhaps the simplest way to determine globule size distribution is by optical microscopy; but, although it is most tedious and lengthy, it is also inexpensive and direct. The emulsion is diluted in a medium and examined under a light microscope. At least 500 globules should be counted and classified either by direct viewing or from a projected image (Harkins et al., 1929), or from photomicrographs (Cooper, 1937). To reduce the tedium of visual counting, some mechanical methods have been proposed and used, such as double-image microscopy (Barnett et al., 1962). Although this technique suffers from the disadvantages of microscopy, e.g. the difficulty in sizing globules less than 2 μ in diameter (Van Kreveld, 1942; Saylor, 1965) it provides better

accuracy. Due to invisibility of sub-micron particles, care must be taken to estimate them whenever possible. However, if a log-normal distribution of globule size can be assumed, the loss count may be estimated (Cooper, 1937; King, 1941; Sherman, 1963; Sherman, 1968; Groves et al., 1968).

Electron microscopy is the only direct method to measure droplets of less than 1 μm diameter (Groves et al., 1968), but Walton (1947) noted that major difficulties occur with sampling, the effects of drying under vacuum and the local heating effects of the electron beam. Although, in recent years, freeze-etching has been used to prepare the specimen, larger drops could be missed owing to the small field of view.

The Coulter Counter is one of the alternative methods which can be used to study emulsion stability (Higuchi, Okada and Lemberger, 1962; Higuchi et al., 1963; Shotton and Davis, 1967; Singleton and Brown, 1965; Halworth and Carless, 1972). This instrument covers approximately the same size range as the optical microscope, but it is statistically more accurate because it is able to classify large numbers of drops quickly. On the other hand, Groves et al. (1968) reported that coalescence and aggregation could be caused by dilution with electrolyte, and that these two effects could not be differentiated by the instrument. Another disadvantage of the method was demonstrated by Shotton and Davis (1968) who emphasised that an oil phase could dissolve in the electrolyte, but they suggested that it could still yield a useful data for the interpretation of the size distribution.

Various other photometric methods have been suggested for globule size determinations. Lloyd (1959) reported that there was a relationship between the reflectance and the surface mean particle diameter. Akers and Lach (1976) have reported a good correlation with other methods and diffuse reflectance spectroscopy and stated that it could be used as a supportive method, offering simplicity and expedience, with other methods to evaluate emulsion stability and drug stability within the emulsion.

Other photometric methods consist of the measurement of transmitted and scattered light (Groves et al., 1968; Livesey and Billmayer, 1969; Monk, Matijevic and Kerker, 1969). Measurements of low-angle scattered light yields only a mean particle diameter (Monk et al., 1969) and a high degree of dilution may present a problem. However, use of transmitted light permits measurement with more concentrated emulsions. The determination of specific interfacial area (Langlois et al., 1954) as well as average droplet size (Osipow, Birsan and Snell, 1957) have been reported. Turbidity measurements have also been performed to estimate the globule size distribution of emulsions. Goulden (1961) used this technique for the first time in systematic studies to determine size distribution in milk. Wallach et al. (1961) and Walstra (1968) observed that spectroturbidimetry was very sensitive to changes in drop size and distribution and the results agreed with those determined with a Coulter Counter and the microscope for the drop diameters of 0.2 to 15 μm. Recently, Reddy et al. (1981a) developed a novel technique using the relationship

between turbidity, particle size and concentration. The results were in excellent agreement with results from scanning electron microscopy.

Droplet diameter can be determined by sedimentation methods based on the relationship between the diameter of the spherical particle and the rate of sedimentation under gravity (Becher, 1965; Kaye and Seager, 1965 and 1967). However, Groves et al. (1968) stated that particles under 10 μm diameter cream very slowly under gravity and displacement currents as well as Brownian movement all tend to disturb the sedimentation pattern. Therefore, increasing the settling rate by centrifugation was necessary and since 1951, when Kamack centrifuged powder dispersions, this technique has been used. The requirement for complete determination for each point on the cumulative distribution curve was the biggest disadvantage, but a modified disc centrifugal photosedimentometer was developed and used by Groves, Kaye and Scarlett (1964). The emulsion was centrifuged in a hollow perspex disc and the concentration of droplets at a given radius was measured photometrically. This technique has been widely used since then and several modifications have been made to improve the technique, its theoretical background being well documented (Garret, 1962; Parkinson, Matsumoto and Sherman, 1970; Matsumoto and Fukushima, 1974; Groves and Yalabik, 1975 a and b).

1.4.2.3 Other methods of assessing emulsion stability

Measurement of electrical properties, such as electrophoretic mobility, can be used to test stability when electrostatic double-layer repulsion is of primary importance.

Electrophoresis measurements yield a parameter known as the zeta potential, which is defined as the potential difference between the surface of the tightly bound layer (shear plane) and the electroneutral region of the solution,can be related to the double layer potential (Becher, 1965). The zeta potential is actually smaller than the double-layer potential (Overbeek and Lijklema, 1959) because it is not measured at the interface but is measured at the "shear plane" which is at a greater distance from the particle than the boundary of the double-layer. When an emulsion is subjected to an electric field, the droplets will move towards one of the electrodes depending on the charge, the velocity being related to the magnitude of the charge density (Becher, 1965; Sherman, 1968). A number of publications have discussed the correlation between zeta potential, the rate of coagulation, mean globule diameters, the extent of adsorption and desorption of the emulsifier during ageing (Becher, 1965; Dorle and Rambhau, 1972; Kitchener et al., 1968; Rambhau, Phadke and Dorle, 1977).

If the interfacial film is the principal barrier to coalescence, interfacial rheometry may be a more suitable means to investigate the stability of an emulsion. Some of the work on the stabilizing effects of an interfacial film has already been discussed (pages 29-30) and methods of measuring the rheological properties of interfaces have been reviewed (Becher, 1965; Sherman, 1968; Boyd et al., 1976; Sherman et al., 1980). The relationship between spreading coefficient, HLB, PIT and emulsion stability has been discussed on pages 30-31 and this can also be used to evaluate the stability of the emulsions.

It is possible to calculate the total interfacial area from an analytical estimation of the amount of surfactant adsorbed by the emulsion droplets. Knowledge of the area of interface occupied by each surfactant molecule is required and the average droplet diameter can be calculated from the volume of the oil (Vold and Mittal, 1972 and 1973; Becher, 1965; Groves et al., 1968), but no information about size distribution can be gleaned.

1.4.2.4 Accelerated stability testing of emulsions

The purpose of an accelerated stability test is to increase the stresses upon a product and attempt to predict whether or not it will withstand the more normal stresses under usual conditions of storage for a sufficiently long period of time. For this procedure to be valid it must only accelerate the process of instability and it should not alter it. Accelerated stability testing of emulsions has been reviewed by Groves (1970) and Sherman (1971).

Centrifugation and abnormal temperatures have frequently been used as accelerating stresses. Three methods of inducing temperature stress are used, exposure to elevated or low temperatures and temperature cycling. In general, elevated temperature leads to instability of emulsions but there is no simple correlation with normal storage conditions. Bennett et al. (1968) stated that an increase of 10°C in the temperature can be considered to double the rate of most reactions. Therefore, three months at 45-50°C is equivalent to one year at 20-25°C for many systems. This may be true, but it must be proven that the higher storage temperature only accelerates the mechanism of instability which operates

at the lower temperature. According to Bennett et al. (1968), heating lowers the viscosity of the external phase of the emulsion and may even cause discontinuities at the interfacial film and change the solubility balance of the surfactant in both phases. If this is so, heating not only accelerates the normal process of instability, but the emulsion may invert at the higher temperature (PIT) due to change in emulsifier distribution (Shinoda and Arai, 1964; Shinoda and Saito, 1969).

Exposure to low temperatures can also cause changes in the solubility pattern of the emulsifier. When an o/w emulsion is frozen, water crystals in the external phase push the oil droplets closer to each other until they coalesce or aggregate (Groves, 1970). The lipophilic portions of the emulsifier molecules lose their mobility due to the surrounding ice and hydrophilic portion is dehydrated because of the freezing out of water. Thus, the interfacial film is weakened. As well as formulation factors, the freezing rate is important and determines whether the system will recover the original form on thawing.

Temperature cycling has been used for stability testing of pharmaceuticals for some time. Groves (1970) stated that one of the most effective methods of cracking an emulsion was to cycle it between two extremes of temperature, the stability of an emulsion to alternate freezing and thawing being reviewed by Sherman (1968). Carless and Hallworth (1966) and Varney (1967) have observed crystal growth in suspensions when exposed to temperature-cycling conditions. This was due to Ostwald ripening in

which the smaller particles completely dissolved at the higher temperatures, and the solute then crystallized on to the large particles at lower temperatures. Emulsion droplets could coalesce by a similar process, by molecular diffusion or through discontinuities and weakening of the interfacial film caused by temperature cycling.

Centrifugal stress is a widely used technique in emulsion stability testing. Merrill (1943) subjected emulsions to centrifugal forces of up to 3600 rev/min and by measuring the separation of the oil, he showed that the age of the emulsion affected the rate of separation. Smith and Grinling (1930) and Cockton and Wynn (1952) used the centrifuge to evaluate instability and measured the drop size distribution with a microscope after centrifugation. Both groups of workers observed an absence of a simple correlation between the behaviour of an emulsion in the centrifuge and its behaviour under storage conditions.

Many emulsions are too stable to exhibit separation in the laboratory centrifuge (Groves, 1970) and so the ultracentrifuge has been used for this purpose (Garrett, 1962 and 1970; Vold et al., 1972 and 1973), but it only provides information on the coalescence process. The centrifuging of an emulsion is a different physical state from a system under gravitational stress because the drops are very closely packed compared with normal conditions. It is therefore unlikely that a centrifugal method can be used to determine the ageing behaviour of emulsion under normal conditions. Garrett (1970) suggested that the results could be related to the film strength, only the

initial rate of oil separation being related to drop size. The film may have a yield stress that can be exceeded by stress in the ultracentrifuge but not by normal gravitational stress. By observing the amount of free oil at varying speeds, the pressure required to cause coalescence can be obtained. This gives a measure of the strength of the interfacial barrier (Smith and Mitchell, 1976).

1.5 Phase equilibrium studies

Phase equilibrium studies have frequently been employed in an attempt to understand emulsion stability where complex interactions exist between water, oil and surfactants in various compositions (Burt, 1965; Lachampt, 1967; Swarbrick, 1968; Friberg et al., 1970a; Treguier et al., 1975; Lo et al., 1977). The formation of liquid crystalline phases from the three components can improve the stability of the emulsion (Friberg and Wilton, 1970b; Friberg, 1971; Friberg, Jansson and Lederberg, 1976; Fukushima, Yamaguchi and Harusawa, 1977) where a tendency to form a layered structure in the thin region between two approaching droplets will give stability against coalescence (Friberg et al., 1970b). The relationship between the phase distribution of the components and the nature and properties of a dispersion formed in these water-oil-emulsifier systems can be evaluated (Mulley and Marland, 1970; Marland and Mulley, 1971; Ali and Mulley, 1978; Lo et al., 1977).

The various phases that are usually observed with three or four components are: isotropic micellar phases, liquid crystalline phases and emulsion phases. A micellar solution consists of a dispersion of colloidal-sized

aggregates of surfactant molecules as first noted by McBain (1950). When the concentration of the surfactant reaches the critical micellar concentration (CMC), micelles start forming and are thermodynamically stable (McBain, 1950). The micellar phase shows a pronounced Tyndall effect and is isotropic when observed in the polarizing microscope. The term isotropic means that the optical properties are the same in every direction.

The liquid crystalline phases or mesophases may be recognized macroscopically by their visual appearance and their greater viscosity compared with that of water, ranging from mobile liquids to rigid gels, and microscopically by birefringence because of their highly oriented molecular structure which shares some of the properties of both liquids and soilds. Such substances may flow like a liquid, while possessing many of the optical properties of a solid. Liquid crystals are optically anisotropic (Rosevear, 1968; Ekwall, 1975) showing birefringence when observed between crossed polarizers in a microscope. Some gels, however, do not appear to exhibit such characteristics under microscopic examination (Ekwall, 1975; Winsor, 1968; Lachampt, 1967).

The existence of mesophases in three component systems and their representations in triangular phase diagrams have been extensively investigated and recorded by Ekwall and co-workers (Ekwall, 1975). The interesting result observed is that the lyotropic mesophases conform to the phase rule, thus in a three component system there are never more than three phases present and this is interpreted as proof that the mesophases are genuine homogeneous phases and not dispersed emulsions (Ekwall, 1975).

The existence of liquid crystalline phases in two, three and four component systems has also been demonstrated by several researchers (Lawrence, 1958; Barry and Eccleston, 1973; Lachampt, 1967; Ali et al., 1978; Lo et al., 1977). Liquid crystals may form at very low surfactant concentrations when long-chain alkanols are incorporated and these may even be below the CMC of the binary surfactant-water system (Ekwall, 1975). Mulley (1964) suggested that this was due to the reduction in repulsive forces between ionic head groups and the strong interaction of hydrocarbon chains.

Only a few ternary (Ekwall, Mandel and Fontell, 1970; Fontell, 1973; Friberg and Wilton, 1970b; Friberg, 1979; Friberg et al., 1969; Mulley et al., 1964; Treguier et al., 1975) and quaternary (Mulley and Marland, 1970; Marland and Mulley, 1971; Ali et al., 1978; Lo et al., 1977; Adrangui et al., 1979) systems of water-oil-non-ionic surfactants have been investigated. Most other studies have been made on binary and ternary systems containing ionic surfactants (Ekwall, 1975). The recent increase in the study of non-ionic surfactants is mainly due to their interesting interactions with water and hydrocarbons, their generally low toxicity, and potential as models for biomembranes (Dervichian, 1977).

Examination of published triangular diagrams shows that regions in which only two liquids co-exist are often confined to very low surfactant concentrations, thus it may be concluded that many emulsions are not simply liquid in liquid dispersions but are in fact liquid crystals plus one or more liquid phases. The postulate of Schulman et al.

(1940) that emulsions are two liquid systems stabilized by monomolecular films is probably not applicable to many emulsions, and it has been postulated that emulsions containing mesophases are much more stable than those without them (Friberg et al., 1970; Friberg, 1979; Fukishima et al., 1977).

Many systems containing surfactants show similar features, the L_1 region being an aqueous micellar phase, in contrast to the L_2 which is a continuum of organic compound with water within micelles (reversed micelles). Towards one side of the triangle liquids L_1 and L_2 co-exist but at higher surfactant concentrations, liquid crystalline (LC) phases may be present, either alone or co-existing with L_1 and L_2 or solid. The occurrence of LC phases and the area of a phase diagram occupied by such mesophases, is dependent upon the nature, notably the hydrophilic chain length of both surfactant and oil (Marland et al., 1971, Lo et al., 1977). However, some of the shorter chain length non-ionic surfactants do not form liquid crystals at all, even in the presence of polar additives (Mulley et al., 1964).

Ekwall (1975) and Winsor (1968) have reviewed most of the ternary phase diagrams published in the literature and summarized the properties and identification of various mesophases together with their terminology.

1.6 Diffusion

1.6.1 Theory of diffusion

Diffusion is the process by which matter is transported from one part of a system to another as a result of random molecular motions. In any finite time and in every part

of the system component molecules move along every vector of a three-dimensional coordinate system, and a net mass movement results from a concentration gradient. In other words, diffusion is a process which leads to an equalization of concentrations within a single phase as a result of a random Brownian movement (Crank, 1975; Jost, 1960; Flynn, Yalkowsky and Roseman, 1974).

Diffusion is an irreversible process, involving a decrease in free energy at constant temperature and pressure. Fick (1855) derived a general diffusion law governing linear diffusion which stated that the rate of diffusion is proportional to the chemical potential gradient which, for an ideal solution, is equal to the concentration gradient. This law is usually referred to as Fick's first law of diffusion and expressed for net diffusion in direction x as

$$J = -D \frac{dC}{dx} \qquad (1.1)$$

where J is the flux of the material across a unit area of film, D is the diffusion coefficient and (dC/dx) is the concentration gradient. The negative sign implies that the material flows from an element of higher concentration to an element of lower concentration.

Although Fick's first law is a concise mathematical statement, it is not directly applicable to the solution of most permeation problems. It contains three principal variables, J, C and x. Further, J itself is a multiple variable. The number of variables is reduced in Fick's second law, which is the fundamental mathematical statement of diffusion and is a useful form resolving most diffusion

problems. Fick's second law is given for the unidimensional flow case as:

$$\frac{dC}{dt} = D\frac{d^2C}{dx^2} \tag{1.2}$$

where the symbols have the same meaning as equation (1.1).

When a membrane is introduced between the solution of the penetrant and the solvent, initially a non-steady state exists where both the rate of flow and concentration at any point in the membrane changes with time. This "lag period" continued until the steady state is reached when the amount leaving the membrane is equal to the amount entering. Here there is no change in concentration at any given point in the membrane and

$$\frac{dC}{dt} = 0 \tag{1.3}$$

When either the applied phase and/or the receptor phase concentrations vary with time, the mathematical analysis is considerably more complicated. After some finite time an instantaneous or quasisteady state develops and the time course for the diffusional process is initiated and followed after the onset of the quasisteady state. Requisite to successful analysis of these situations are the following conditions:

(1) The gradient within the membrane must instantaneously adjust to the external conditions.

(2) The amount (not concentration) of diffusant in the membrane must be negligible.

When the conditions are such that there is a linear fall of concentration within the barrier, the instantaneous

concentration gradient may be expressed by

$$-\frac{dC}{dx} = \frac{C_o - C_h}{h} \qquad (1.4)$$

where C_o and C_h are the respective concentrations of the membrane.

The mathematical treatment of a diffusion process depends upon the model chosen for the particular investigation, detailed mathematical treatment of various transport phenomena being covered by Jost (1960), Crank (1975), Tuwiner (1962).

1.6.2 Methods of studying diffusion

Methods have been devised to measure the diffusion coefficient in various systems. All methods are subject to sources of error as well as to limitations in the concentration ranges over which they yield reliable results. The apparatus chosen should be such that the variables of time, concentration, and distance can be accurately checked throughout the diffusion process. In addition, there may be the need for stirring to reduce the effect of stagnant film layers which would otherwise cause an additional resistance to diffusion on either side of the membrane. The possibility of volume changes also exists. Further, either sink or non-sink conditions may be used experimentally. In the former, the concentration of the diffusant in the receptor is kept very low or zero to avoid the reduction of the concentration gradient or production of reverse diffusion currents.

Data from such diffusional experiments have been used to determine the diffusion coefficients using one of the

basic mathematical forms from the basic diffusion equations. Different types of experimental methods have been covered by Jost (1960), Tuwiner (1962), Crank and Park (1968).

1.6.2.1 The steady state method

A steady state is reached after a time when the diffusion takes place through a plane sheet or membrane of thickness, h, whose surfaces, x=o, x=h, are maintained at constant concentrations C_1,C_2 respectively. Provided the diffusion coefficient, D, is constant, then from Fick's law

$$\frac{d^2C}{dx^2} = 0 \qquad (1.5)$$

By integrating the equation twice with respect to x and introducing the conditions x=o, x=h, we obtain

$$\frac{C-C_1}{C_2-C_1} = \frac{x}{h} \qquad (1.6)$$

where h is the thickness of the membrane, whose surfaces x=o, x=h are maintained at constant concentrations C_1 and C_2 respectively, and C is the applied concentration. This indicates that the concentration varies linearly through the membrane from C_1 to C_2. The rate of transfer of diffusant, dM/dt, is the same across all sections of membrane given by

$$\frac{dM}{dt} = -D\frac{dC}{dx} = -D\frac{(C_1-C_2)}{h} \qquad (1.7)$$

If the thickness, h, and the surface concentrations C_1 and C_2 are known, D can be deduced from one single experimental determination of the diffusion flux, $\frac{dM}{dt}$.

If the diffusion coefficient varies with concentration, the value of D deduced from a measurement of the diffusion

flux is some kind of mean value. If D is a function of C,

$$\frac{dM}{dt} = -D\frac{dC}{dx} = \text{constant} \qquad (1.8)$$

still holds. Barrer (1946) has pointed out that the concentration dependence of D can be deduced from a single experiment using equation (1.8), provided the concentration distribution through the membrane in the steady state is observed as well as the flux.

1.6.2.2 The time lag method

1.6.2.2.1 Constant D

Prior to the establishment of a steady state, both the rate of flow and the concentration at any point of the membrane vary with time. If the diffusion coefficient is constant, the membrane is initially free of the diffusant and the diffusant is continuously removed from the receptor side (C_2=0), the amount of diffusant, M(t) passing through the membrane in time t is given (Jost, 1960; Crank et al., 1968; Rogers et al., 1954; Flynn et al., 1974) by

$$\frac{M(t)}{hC_1} = \frac{Dt}{h^2} - \frac{1}{6} - \frac{2}{x^2}\sum_{n=1}^{n=\infty}\frac{(-1)^n}{n^2}\exp\left(\frac{-Dn^2x^2t}{h^2}\right) \qquad (1.9)$$

where h is the thickness of the membrane,

C_1 is the concentration at the membrane surface adjacent to the donor phase and D is the diffusion coefficient. As $t \to \infty$, the steady state is approached and the exponential terms become negligibly small, so that the graph of M(t) against t tends towards linearity:

$$M(t) = \frac{DC_1}{h}\left(t - \frac{h^2}{6D}\right) \qquad (1.10)$$

which, on differentiation, yields equation (1.7). If C_2 is zero, giving an intercept, L, on the t axis known as lag time (Barrer, 1957):

$$L = \frac{h^2}{6D} \qquad (1.11)$$

Therefore, knowing L from permeation measurements, D can be calculated from equation (1.11).

1.6.2.2.2 Variable D

The relationship between the diffusion coefficient and concentration must be of a known form or be assumed to satisfy an arbitrary analytical expression containing unknown parameters. If the relationship is known to be of the form $D = D_o e^{\beta C}$, the values of D_o and β are determined from a series of measurements of the lag time (Frisch, 1957).

For the boundary conditions

$$C=C_o,\ x=0,\ t > 0$$

$$C=0,\ x=h,\ t > 0$$

$$C=0,\ 0 < x < h,\ t=0$$

Frisch (1957) shows that the time lag, L, is given by

$$L = \frac{\int_o^t x C_s(x)\,dx}{\int_o^t D(C)\,dC} \qquad (1.12)$$

where $C_s(x)$ is the concentration distribution in the steady state and, in principle at least, can be found from equation (1.13):

$$\int_{C_s}^{C_o} D(C)\,dC = \frac{x}{h} \int_o^{C_o} D(C)\,dC \qquad (1.13)$$

1.6.2.2.3 Short time approximation

In circumstances where diffusivities are very small or membranes are very thick, extremely long times are required to attain steady-state conditions and diffusional runs are very lengthy which are at least analytically inconvenient. All equations based on the series converging at large values of time would be dubious if not totally inapplicable under these circumstances. An alternative method to the solution of equation (1.11) has been suggested (Rogers et al., 1954; Short et al., 1970; Flynn et al., 1974), which takes a simple form at short times and is termed the small times approximation. A solution for gaseous systems with a constant D is given as:

$$\frac{dP}{dt} = \left(\frac{2ASP_1}{v}\right)\left(\frac{D}{\pi t}\right)^{\frac{1}{2}} \sum_{m=0}^{m=\infty} \exp\left[-\left(\frac{h^2}{4Dt}\right)(2m+1)^2\right] \qquad (1.14)$$

where S is the solubility, P the pressure at the donor phase, dP/dt, the rate of increase in pressure in an initially evacuated vessel of volume, v, due to the vapours leaving a face of the membrane of area A, and thickness, h, the other face being in contact with vapour at a constant pressure, P_1. A similar treatment may be used substituting concentration for pressure in liquids.

When t is sufficiently small, only the first term in the series of exponentials in equation (1.14) is important and equation (1.14) then reduces to:

$$\ell n\left(t^{\frac{1}{2}}\frac{dP}{dt}\right) = \ell n\left[\left(\frac{2ASP_1}{v}\right)\left(\frac{D}{\pi}\right)^{\frac{1}{2}}\right] - \frac{h^2}{4Dt} \qquad (1.15)$$

By plotting the quantity on the left side of equation (1.15) against the reciprocal of time, a straight line is obtained from whose slope D can be calculated where

$$\text{Slope} = -\frac{h^2}{4D} \qquad (1.16)$$

Rogers er al. (1954) and Flynn et al. (1974) have defined the applicability of the short-time and long-time approaches as 2.7 x lag-time. This implies that the limit of the short-time approach is 2.7 x lag-time which is about the onset of the steady-state and the beginning point of the applicability of the long-time converging equation.

1.7 Release from emulsified systems

In a series of papers, the rates of transfer of several drug molecules between water and several organic phases have been investigated in order to explain the mechanism of the release from emulsified systems.

The effect of the partition coefficient, the volume fraction of the phases, and the particle size on diffusional movement of a medicament through heterogeneous barriers has been investigated by a number of workers (Higuchi and Higuchi, 1960; Higuchi, 1962; Higuchi, 1964). These reported that there was a good agreement between the theoretical calculations and experimental results. Koizumi and Higuchi (1968 a and b) tested the validity of the "square root" relationship for concentration dependent diffusion and the applicability of the Bruggeman and Wagner-Wiener equations and found that the Bruggeman equation was better than the other. Goldberg et al. (1967) and Goldberg and Higuchi

(1969) have given the mechanism of the interfacial transport of micelle solubilized 2,3-bis-(p-methoxyphenyl)indole and dibutyl phthalate using emulsified oil droplets as the sink. The equations used to calculate the theoretical calculations were based on first principles of diffusion and considered for two separate cases, that of a simple diffusion and of an electrical barrier to the transport process (Goldberg et al., 1967). When experiments were performed, the results were not in good agreement with predicted from these equations, but the theoretical model for an interfacial barrier formed by the surfactant provided the best agreement. Therefore, this model was proposed as the rate-determining mechanism in the transport process (Goldberg et al., 1969). The same technique was used to investigate the influence of gelatin adsorbed at the oil/water interface upon the transport rate of diethyl phthalate (Ghanem, Higuchi and Simonelli, 1969, 1970 a and b) and ^{14}C labelled cholesterol, octanol and progesteron (Ghanem et al., 1970b). In all cases the rates of solute release from gelatin coated droplets were slower than that of the diffusion controlled release rates. Yotsuyanagi et al. (1973) have also summarized the theoretical considerations and some of their experimental results on the transport of solutes through an interfacial barrier at the oil/water interface, and the effects of the variables such as phase volume fraction, partition coefficient and particle size of droplets. Surpuriya and Higuchi (1972 a and b) have looked at the interfacially controlled transport of micelle solubilized sterols and their data strongly supported the previously proposed transport mechanism of

solutes across an oil/water interface that the transport is

(1) interfacially controlled, and

(2) involves a two-step process in which there is first a collision of the solute-micelle complex with the oil/water interface, followed by the release of the solute from the micelle in a largely polar environment at the interface.

Another alternative mechanism based upon a slow rate of solubilization in the aqueous diffusion layer was also considered but experimental data again favoured the interfacial resistance hypothesis (Gatmaitan, Yotsuyanagi and Higuchi, 1977).

The experimental technique used in these investigations was almost the same in that either the emulsified oil droplets were used as sink with the external phase being used as a drug carrier or vice versa, and that the increase or decrease in concentration of the solute in one of these phases was monitored with time. There was no other artificial membrane involved in the process. Howard et al. (1969 a and b) placed the lipid phase which was used as a sink at the bottom of the container and layered the aqueous or the micellar phase on top and suggested that this system provided a constant oil/water interface. A similar method was employed by Windheuser, Best and Perrin (1970), but the drug was incorporated in a w/o emulsion which was placed on top of an aqueous receptor phase. Windheuser et al. (1970) examined the effects of pH, barrier layer thickness, viscosity of the oil and phase volume ratios and reported that the sustained release pattern could be effected by changing these variables. Waggoner and Fincher (1971) used

dialysis membrane to separate the emulsion donor cell and an aqueous receptor cell similar to Koizumi et al. (1968 a and b) and looked at the effect of HLB when comparing the release rates of ephedrine from the emulsions, oily and aqueous solutions. Their results supported evidence for the existence of an interfacial barrier at the oil/water interface and that the release rate was affected by the HLB of the surfactant systems used (Waggoner et al., 1971). Brodin and co-workers (Brodin and Agren, 1971; Brodin and Nilsson, 1973; Brodin, 1974 and 1975; Brodin, Sandin and Faijerson, 1976) employed another method in their studies in that a thermostatted glass column was filled with the continuous phase and that the drops of the disperse phase were formed by an automatic burette and passed through the column. The drug to be transported was in one of these phases and the collected drop phase after passing the column was monitored using a UV spectrophotometer. Transfer between drops and continuous phase was measured in both directions. They divided the transport of a solute between two immiscible liquid phases into three steps;

(1) Solute is transported to the inferface by diffusion and circulation,

(2) there is resolvation of solute molecules in the interface, and this is followed by

(3) the solute being transported from the interface to the bulk of the second phase by diffusion and circulation.

Step (2) is a measure of the transport of a molecule between two phases and it was found that there was a linear relationship between resolvation rate constants and the partition coefficients (Brodin et al., 1973; Brodin 1974 and 1975; Brodin et al., 1976).

1.8 Scope of the thesis

During the past few decades there have been numerous attempts to control the release of drugs from various types of dosage forms and hence optimize their therapeutic effect. Reports in the literature (pages 1-25) have indicated that they have already been used as drug delivery systems. The purpose of this study is the development of stable oil-in-water emulsions so that the parameters which control the release of drugs from emulsions can be investigated. Therefore, Miglyol-812 which was found to be useful in the production of pharmaceutical and cosmetic products, will be used as the oil phase and the ternary phase diagrams will be studied initially with anionic, cationic and non-ionic surfactants in an attempt to determine some fundamental information concerning the stability of the emulsions produced. Candidate emulsions will then be tested for their stability in the presence of drug and various additives and release characteristics of these emulsions will be evaluated.

Although the true partition coefficient is not changed, the change in apparent partition coefficient may alter the drug release. This will be studied by varying the surfactant concentration which might affect the distribution of the drug in the oil, aqueous and micellar phases of the emulsion. The oil/water volume ratio of an emulsion also affects the distribution of the drug in various phases of the emulsion. Therefore, the effect of phase volume ratio on drug release also will be investigated. Another parameter which again affects the apparent partition coefficient, pH, will also be studied. By changing the pH of the emulsion during the

release experiment, partitioning of the drug might be affected so that the release characteristics may change. The effect of pH is also important with respect to administration since it would suggest that release rates would vary during passage through the gastro-intestinal tract.

Considering the interfacial film, covering the oil globules, as a barrier to drug release, the effect of the nature of this film will be investigated by changing the surfactant used to stabilize the emulsions. Then, different drugs will be incorporated in a model emulsion and the effect of the partition coefficient on drug release will be studied. The release of these drugs from emulsions will also be compared with the release from the aqueous and oily solutions. Lastly, the effect of some additives, gelling agents, will be studied in order to investigate the effect of the viscosity of the oil phase on drug release.

Long term and elevated stability tests will be performed with a group of emulsions which will be prepared with cetomacrogol at varying concentrations. Particle size distribution, electrophoretic mobility, creaming rate and the viscosity of the emulsions will be determined under normal storage conditions or at 40°C. The effect of ageing on the stabilities and the release characteristics of these emulsions will be studied up to 6 months.

CHAPTER 2

MATERIALS AND METHODS

2.1 Materials

The following materials were used as received from the commercial supplier or manufacturer without further purification.

2.1.1 Oils

Miglyol-812 Neutral Oil, Triglyceride of fractionated coconut oil fatty acids C_8-C_{10}.

(Dynamit Nobel (UK) Ltd., Slough, Berks.)

Miglyol-829, Triglyceride of fractionated coconut oil fatty acids C_8-C_{10}, and succinic acid.

(Dynamit Nobel (UK) Ltd., Slough, Berks.)

2.1.2 Surfactants

Texafor AIP (Cetamacrogol-1000, B.P. 1973).

(A.B.M. Chemicals Ltd., Cheshire)

Sodium Lauryl Sulphate.

(BDH Chemicals Ltd., Poole)

Tween 20, Polyoxyethylene (20) Sorbitan Monolaurate.

(Atlas Chemical Industries (UK) Ltd., London)

Span 80, Sorbitan Monooleate.

(Atlas Chemical Industries (UK) Ltd., London)

2.1.3 Gelling agents

Miglyol-Gel, Miglyol 812 Neutral Oil gelled with an organically modified montmorillonite (Bentone).

(Dynamit Nobel (UK) Ltd., Slough, Berks.)

Aerosil 200, Colloidal silicon dioxide.

(Bush, Beach and Segner Bayley Ltd., London)

Aerosil 300, Colloidal silicon dioxide.

(Bush, Beach and Segner Bayley Ltd., London)

Bentone 34 and 38, Organic montmorillonite.

(Steetley Minerals Ltd., Worksop, Notts.)

2.1.4 Other materials

Salicylic Acid, Analar Grade.

(BDH Chemicals Ltd., Poole)

Benzoic Acid, Lab. Reagent Grade.

(Hopkin and Williams Ltd., Essex)

m-Hydroxy Benzoic Acid, Lab. Reagent Grade.

(BDH Chemicals Ltd., Poole)

Aspirin, BP. quality.

(Evans Medical Ltd., Liverpool)

Paracetamol, BP. quality.

(Evans Medical Ltd., Liverpool)

Phenacetin, Lab. Reagent Grade.

(BDH Chemicals Ltd., Poole)

Potassium Chloride, Analar Grade.

(BDH Chemicals Ltd., Poole)

Di-Sodium Hydrogen Orthophosphate, anhydrous, Analar Grade.

(BDH Chemicals Ltd., Poole)

Citric Acid, Analar Grade.

(BDH Chemicals Ltd., Poole)

Visking tubing, cellulose acetate membrane, size 36/32.

(Scientific Instrument Centre Ltd., London)

2.2 Methods

2.2.1 Preparation of Miglyol emulsions

The drug was dissolved in Miglyol by heating to 40°C and the surfactant was dissolved in 20 g of water also at 40°C before being added to it. This was mixed for two minutes with a Silverson mixer (Silverson Machines Ltd., Waterside, Chesham, Bucks.) and the remaining water was then added and mixed for another 10 minutes followed by homogenisation 3 times with a laboratory type hand homogenizer (Model URF-1, Ormerod Engineers Ltd., Huddersfield, Yorks.). Emulsions were stored in well-closed 50 ml bottles at 20° ± 2°C (and at 40°C for elevated stability tests). The emulsions were always preheated to 37°C before the release experiments. When oil-soluble surfactants were included in the formulation, they were dissolved in the oil phase together with the drug.

2.2.2 Preparation of oily and aqueous control solutions

The same amounts of surfactant and drug used to prepare 100 ml of emulsion were added to 100 ml of the oil or distilled water to prepare the control solutions. These were always freshly prepared and used within a week, but those containing surfactants were left at least overnight in order to ensure micellar equilibrium before conducting the release experiments. The oily and aqueous solutions of the drugs without surfactants were also prepared and used as control solutions.

2.2.3 Determination of the partition coefficients of the drugs

120 ml containers with a glass tube 0.5 cm in diameter

glued to the inside wall enabled sampling of the aqueous layer without disturbing the interface and were used as the distribution apparatus.

The oil and water phases were prepared exactly as those for emulsions in that the water soluble surfactants were dissolved in the water phase while the oil soluble ones and the drugs were dissolved in Miglyol. A predetermined amount of water phase representing the external phase of the emulsion was poured into the distribution apparatus, and the oil phase was then layered carefully onto the surface of the water phase. The jars were tightly closed and carefully placed in an incubator at 37±1°C without disturbing the interface between the two liquids. The samples were drawn from the water phase at various times and analysed for the drug content. In most cases equilibrium was reached within 14 days, but as a standard procedure in order to ensure equilibrium, samples were withdrawn after 20 days. The samples were collected via the tube from the middle of the aqueous phase in order to give representative samples. After appropriate dilution, the amount of the drug was determined spectrophotometrically at the wavelength of maximum absorbance (λ_{max}) of the drug.

2.2.4 Solubilization of drugs in micellar solutions

The solubilities of drugs at various concentrations of surfactants were studied using the saturation solubility method. Excess drug was added to the surfactant solutions and these were kept at 37°±1°C with occasional shaking until the equilibrium was reached which was tested by analyzing

the samples taken at various times. Equilibrated solutions were filtered through a Whatman filter paper (No. 50) and the amount of the solubilized drug was determined by the spectrophotometric analysis of the filtrates.

2.2.5 Ternary phase diagrams

The ternary phase diagrams were prepared by varying the concentrations of the three components at 10% intervals to cover the whole area of the equilateral triangle. Smaller intervals of 5% and in some cases 2.5% were used to define the limits of the phases.

The mixtures were prepared by weighing the components in glass sample bottles with air-tight caps. To ensure thorough mixing and to enable equilibrium to be reached, the preparations were heated in a shaking water bath to 70°C for at least 3 hours and mixed with a whirlmixer while hot. They were then placed in an incubator at 25±1°C and kept there for a week before the macroscopic and microscopic examinations by which the type of emulsions and/or mesophases were determined.

2.2.6 Determination of emulsion stability

2.2.6.1 Viscosity measurements

The viscosity measurements were performed using a Ferranti-Shirley Cone-plate Viscometer (Ferranti Ltd., Moston, Manchester) at different shear rates. Measurements were made at 25°C using a 20'5" angle cone of radius 3.5 cm. The sweep time used was 240 sec. and the viscosities were measured at maximum shear rates of 1790 sec^{-1} or 17900 sec^{-1}.

2.2.6.2 Particle size distribution measurements

The long-term and accelerated stability of the emulsions were followed by determining their size distribution using both a Fleming-Timbrell Double Image Micrometer (Model A3; Serial No. 3) fitted to a Vickers 4-AW microscope and a Joyce Loebl Disc Centrifuge (Joyce Loebl Ltd., Gateshead, England). Emulsions were diluted in 40% w/w glycerol solution for the microscopic and in water for photosedimentometric analyses.

2.2.6.3 Electrophoretic mobility measurements

The charge on the droplets was determined with a Microelectrophoresis apparatus (Mark I, Rank Bros. Bottisham, Cambridge) in order to determine to what extent it changed during storage and how the charge was related to the stability and the other properties of the emulsions. Experimental detail, such as calibration of the instrument and calculations, will be given in the relevant chapter (Chapter 6).

2.2.7 Drug release experiments

The apparatus shown in Figure 2.1 was used for the release experiments. Visking tubing was soaked in water for at least 16 h, then opened to form a sheet and excess water was removed with tissues before being tightly fixed to the bottom of the donor cell with a heavy duty rubber band. The donor cell was stirred with a glass paddle driven by a motor at 50 r.p.m. while the receptor cell was stirred with a small Teflon coated magnetic bar rotated by an underwater stirrer (Rank Bros., Bottisham, Cambridge). This system was placed

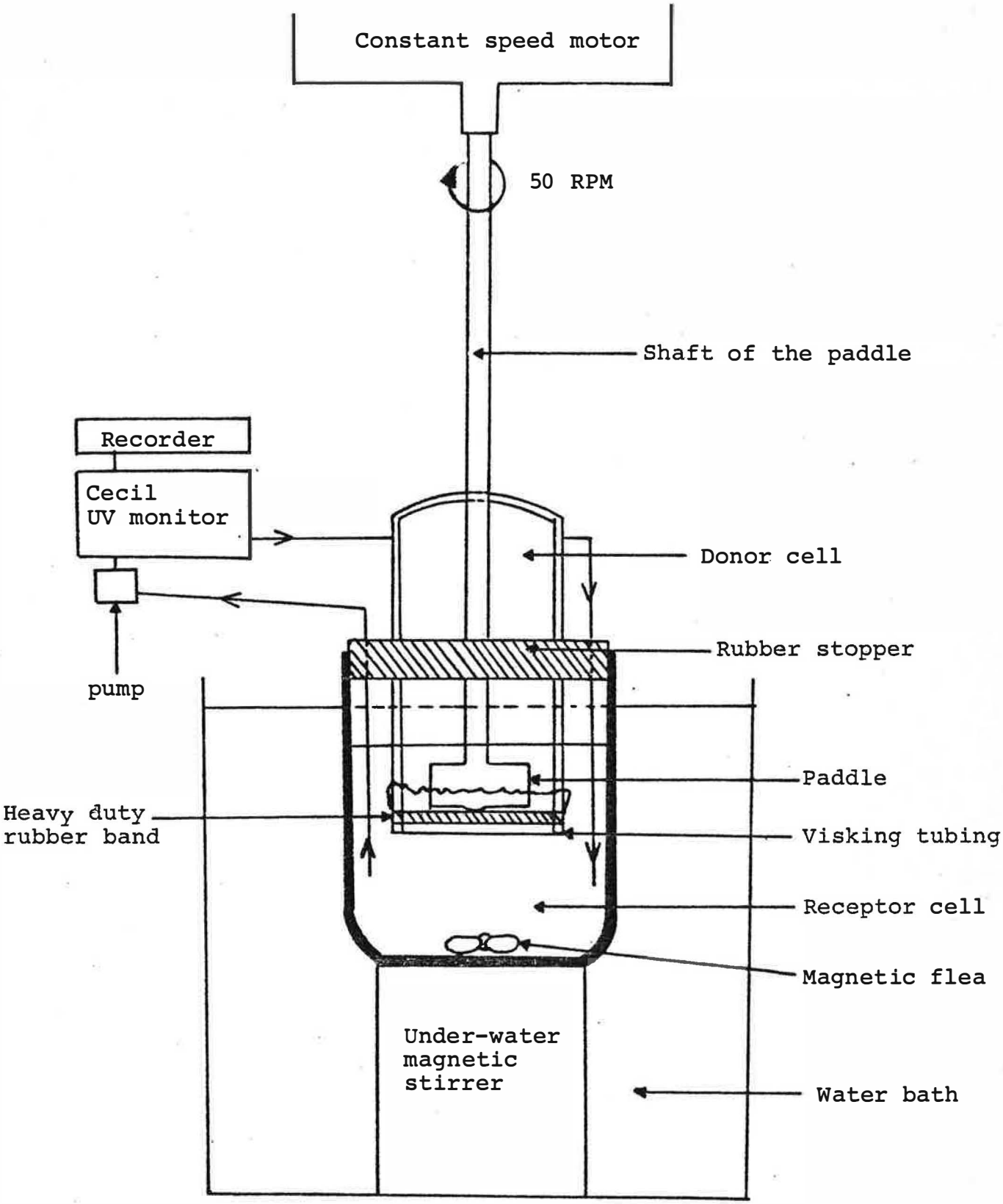


Figure 2.1 . Diagram of the drug release apparatus.

in a water-bath maintained at 37±0.5°C by a water circulator unit (Churchill Instrument Company Ltd., Riverside Way, Uxbridge, Middlesex).

Approximately 10 ml of the pre-warmed emulsion or control solution was weighed in a syringe and introduced into the donor cell. The empty syringe was weighed again to calculate the exact volume of the donor solution from the knowledge of the density, since it was considered that this method eliminated errors due to the effect of viscosity and entrapment of air. Distilled water and McIlvane wide-range buffer solutions (Table 3.3) were used as receptor solutions.

UV absorption of the receptor solutions at the wavelength of maximum absorbance (λ_{max}) of each drug was monitored continuously using a spectrophotometer (Cecil 202, 272) fitted with a 10 mm pathlength flow cell and recorded automatically against time. From these recordings the optical density at given time intervals was determined. All experiments were repeated at least four times and the data given are the mean values ± standard deviations from the mean value.

CHAPTER 3

PRELIMINARY EXPERIMENTS ON DRUG RELEASE

3.1 Introduction

In this chapter are reported the release characteristics of a model drug, salicylic acid, from emulsions and their control solutions. In order to determine the effect of the interfacial film, different surfactants were used to prepare the emulsions and the results are reported together with the effect of the pH of the receptor solution. Apparent partition coefficients of salicylic acid in the absence and presence of the surfactants were determined in oil/water systems representing the emulsions used and these are reported with the theoretical considerations and the calculations.

3.2 Experimental

The drug release experiments and partition coefficient determinations were carried out as described in Chapter 2. Compositions and some physical properties of the emulsions and the control solutions are given in Tables 3.1 and 3.2 respectively. Recorded optical densities were used to calculate the concentration of the receptor solutions at desired time intervals and these were used for the calculations which are given below.

3.3 Theoretical considerations and calculations

3.3.1 Partition coefficient

A drug or a preservative added to an oil/water mixture

Table 3.1. Compositions of emulsions and mixtures used for preliminary release experiments.

% w/w	Em I-1	Em I-2	Em I-3	SA/w	SA/Mig	SA/Cet /w	SA/Cet /Mig	SA/Cet /CSA/w	SA/Cet/ CSA/Mig	SA/SLS /w	SA/SLS /Mig
Water	56.9	54.9	59.6	99.9	-	96.9	-	94.9	-	99.6	-
Miglyol	40.0	40.0	40.0	-	99.9	-	96.9	-	94.9	-	99.6
Salicylic acid	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1
Cetomacrogol 1000	3.0	3.0	-	-	-	3.0	3.0	3.0	3.0	-	-
Cetostearyl alcohol	-	2.0	-	-	-	-	-	2.0	2.0	-	-
Sodium lauryl sulphate	-	-	0.3	-	-	-	-	-	-	0.3	0.3

Table 3.2. Some properties of the emulsions and their control solutions.

	EmI-1	EmI-2	EmI-3	SA/w	SA/Cet /w	SA/Cet/ CSA/w	SA/SLS /w	SA/Mig	SA/Cet/ Mig	SA/Cet/ CSA/Mig	SA/SLS/ Mig
Viscosity at 25°C (cP)	8.5	19.14	5.22	1	1.30	4.17	1.32	22.31	25.50	26.33	22.35
pH	3.45	3.50	3.35	2.5	2.85	2.80	2.75	-	-	-	-

w = Distilled water

Mig = Miglyol-812

Cet = Cetomacrogol-1000

SLS = Sodium lauryl sulphate

CSA = Cetostearyl alcohol

Table 3.3. Composition of McIlvane buffer solutions.

pH	Composition, g/litre	
	Na_2HPO_4 $12.H_2O$	$H_2C_6H_5O_7$ H_2O
2.2	1.43	20.60
3.0	14.70	16.70
5.0	36.90	10.20
7.0	58.90	3.70
8.0	69.60	0.586

partitions itself between the two phases in a definite concentration ratio, provided an insufficient amount is added to saturate the phases. The ratio of the concentrations in the two phases at equilibrium can be represented by

$$\frac{C_o}{C_w} = K \tag{3.1}$$

where C_o = equilibrium concentration in oil phase,

C_w = equilibrium concentration in aqueous phase,

K = partition coefficient.

If a weight M of a drug is added to an oil/water mixture,

$$M = C(V_o+V_w) \tag{3.2}$$

where C = total overall drug concentration in the mixture,

V_o = volume of the oil phase,

V_w = volume of the aqueous phase.

Since $$C_o = K\ C_w \tag{3.3}$$

the weight of the drug in oil phase is

$$C_oV_o = K\ C_wV_o \tag{3.4}$$

and the weight of the drug in aqueous phase is

$$M_w = C_wV_w \tag{3.5}$$

Therefore, $$C(V_o+V_w) = K\ C_wV_o+C_wV_w \tag{3.6}$$

$$= C_w(K\ V_o+V_w)$$

and $$C_w = \frac{C(V_o+V_w)}{K\ V_o+V_w} \tag{3.7}$$

The oil/water ratio is

$$\phi = \frac{V_o}{V_w} \tag{3.8}$$

and $$V_o = \phi V_w$$

Therefore, $$C_w = \frac{C(\phi+1)}{K\ \phi+1} \tag{3.9}$$

or $$K = \frac{C(\phi+1) - C_w}{C_w\phi} \tag{3.10}$$

and $$M_w = M(\frac{1}{K\phi+1}) \tag{3.11}$$

In an emulsion, the drug partitions between the oil, water and the micelles formed by the surfactant. In an aqueous micellar solution,

$$R = \frac{C_w}{C_{free}} \tag{3.12}$$

where R is the ratio of the total/free drug concentration in aqueous phase of the emulsion

$$C_{free} = \frac{C(\phi+1)}{(K_{app}\phi+1)}/R \tag{3.13}$$

and $$C_{free} = \frac{C(\phi+1)}{RK_{app}\phi+R} \tag{3.14}$$

where K_{app} is the partition coefficient of the drug in the presence of the surfactant.

Since $$RK_{app} = K \tag{3.15}$$

equation (3.14) could be rewritten as

$$C_{free} = \frac{C(\phi+1)}{K\ \phi+R} \tag{3.16}$$

Equation (3.16) can be used to estimate the free drug concentration in the aqueous phase of the emulsion, but the surfactant distribution between the aqueous phase, the interface and the oil phase and ionization of the drug has to be considered for accurate calculations. However, if the surfactant is mainly soluble in aqueous phase, $K_{app} < K$ and $C_w > C_{free}$.

3.3.2 Release of the drug

When a thin membrane is used, the gradient within the membrane quickly adjusts to the external phase concentrations and the amount of diffusant in the membrane is negligible (Flynn et al., 1974). Therefore, there is a linear fall of concentration within the barrier and the instantaneous concentration gradient can be expressed by

$$\frac{dC}{dx} = \frac{C_1 - C_2}{h} \tag{3.17}$$

where distance (x) = thickness (h),

or
$$\frac{dM}{dt} = -DA\left(\frac{C_1 - C_2}{h}\right) \tag{3.18}$$

$$dM = V_2 dC_2 \tag{3.19}$$

$$C_1 = \left(C_1^{o} V_1 - C_2 V_2\right)/V_1 = C_1^{o} - C_2\left(\frac{V_2}{V_1}\right) \tag{3.20}$$

therefore
$$C_1 - C_2 = C_1^{o} - C_2\left(\frac{V_2}{V_1}\right) - C_2 \tag{3.21}$$

$$V_2 \frac{dC_2}{dt} = -DA \frac{dC}{dt} = -DA\left(\frac{C_1 - C_2}{h}\right) \tag{3.22}$$

and
$$D\int dt = \frac{V_2 h}{A} \int \frac{dC_2}{C_1^{o} - C_2\left(1 + \frac{V_2}{V_1}\right)} \tag{3.23}$$

which integrates to,

$$Dt = \left(\frac{V_1V_2}{V_1+V_2}\right) \frac{h}{A} \left[\ell n C_1^{\circ} - \ell n\left(C_1^{\circ} - C_2\left(1+\frac{V_2}{V_1}\right)\right)\right] \qquad (3.24)$$

$$= \left(\frac{V_1V_2}{V_1+V_2}\right) \frac{h}{A} \ell n\left[\frac{C_1^{\circ}}{C_1^{\circ} - C_2\left(1+\frac{V_2}{V_1}\right)}\right]$$

and

$$\frac{DA}{h}t = \frac{V_1V_2}{V_1+V_2} \ell n \left[\frac{C_1^{\circ}}{C_1^{\circ} - C_2\left(1+\frac{V_2}{V_1}\right)}\right] = D(f) \qquad (3.25)$$

where C_1° = donor concentration at t=0,

V_1 = donor volume,

C_2 = receptor concentration at time t, and C_2=0 at t=0,

V_2 = receptor volume,

A = area of the membrane,

h = thickness of the membrane.

Therefore a plot of the right-hand side of the equation (3.25) against time yields a straight line with a slope of $\frac{DA}{h}$. As explained in Chapter 2 (2.2.7), the optical density of the receptor solution against time was monitored and these values obtained from the graphs were used to compute the right-hand side of the equation (3.25) using a computer program which, together with the flow diagram, is given in Appendix I. The calculated data was then plotted against time and the slopes of these release curves were determined.

3.4 Results and discussion

The λ_{max} obtained for salicylic acid in distilled water was 297 nm and the calibration curves were in good agreement

with the Lambert-Beer Law. The equations of the calibration lines are given in Appendix II.

Releases from aqueous and oily solutions are shown in Figures 3.1 and 3.2 respectively and the slopes of these lines are summarized in Table 3.4. As can be seen, the release was pH dependent in each case. Although the membrane separated the two cells, it is permeable to the buffer ions as well as the drug, so the pH of the donor solution changed according to the pH of the receptor solutions (Table 3.3). Due to the ionization, the salicylic acid released from aqueous solution decreased with increasing pH in good agreement with the findings of Withington and Collet (1973). These authors reported that the salicylic acid release rate versus pH curve was similar to that of the fraction ionized versus pH curve suggesting a greater degree of interaction of the drug with water at higher pH values. Slower release rates at high pH values were not due to any change in the membrane such as modified porisity, but were due to solute-solvent interaction (Withington et al., 1973). The differences between the slopes corresponding to the pH values of 5, 7 and 8 were not significant as shown in Table 3.4. On the other hand, in the case of salicylic acid release from Miglyol, increasing pH of the receptor solution had an increasing effect on the release as shown in Figure 3.2 and Table 3.4, probably due to the decrease in apparent partition coefficients of the drug with increasing pH values. Doluisio and Swintosky (1964) demonstrated that the apparent transport rate constants of salicylic acid determined at various pH values in a liquid

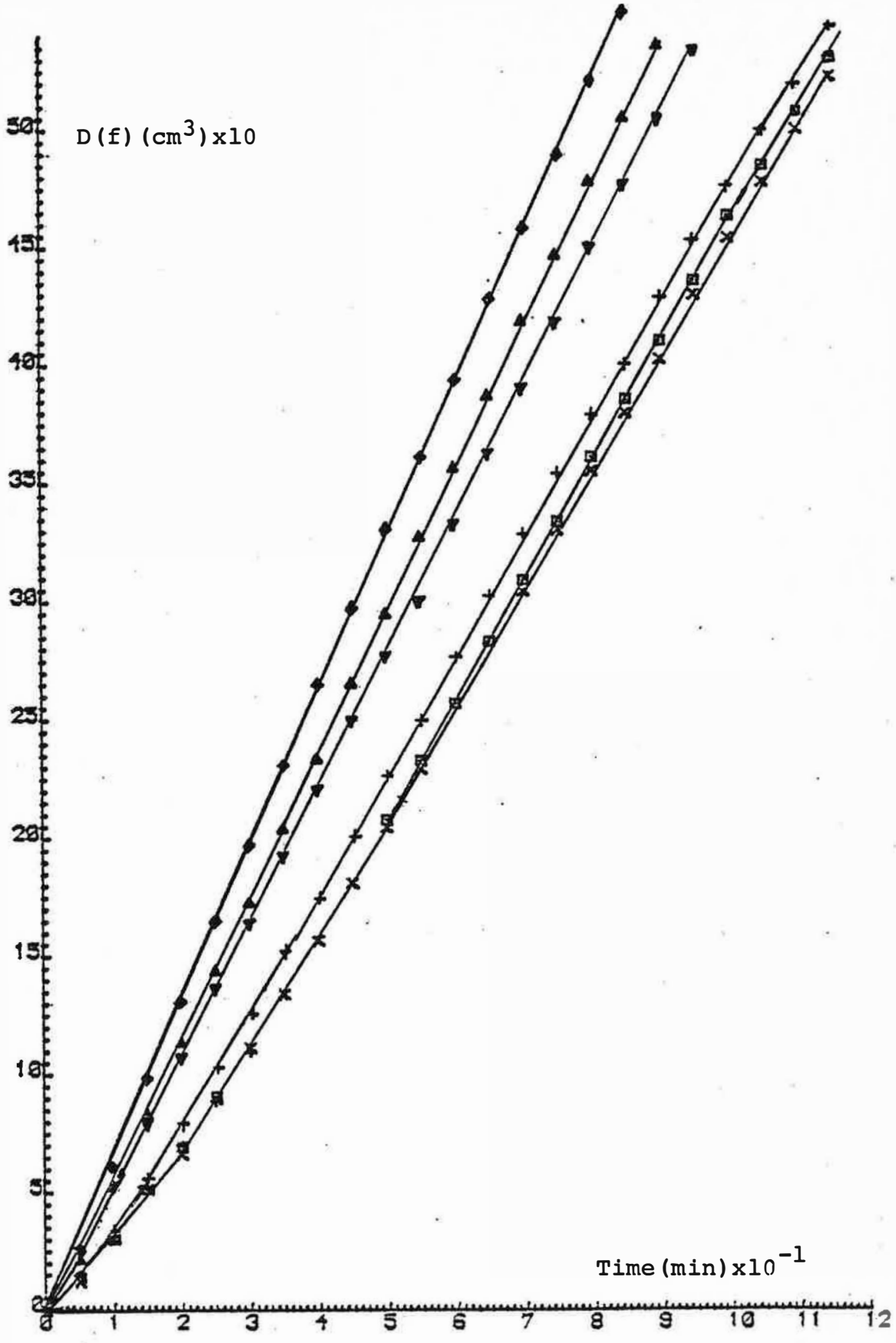


Figure 3.1: Effect of pH on salicylic acid release from aqueous solution. (▲) pH 2.2, (▼) pH 3.0, (+) pH 5.0, (×) pH 7.0, (□) pH 8.0, (◆) distilled water.

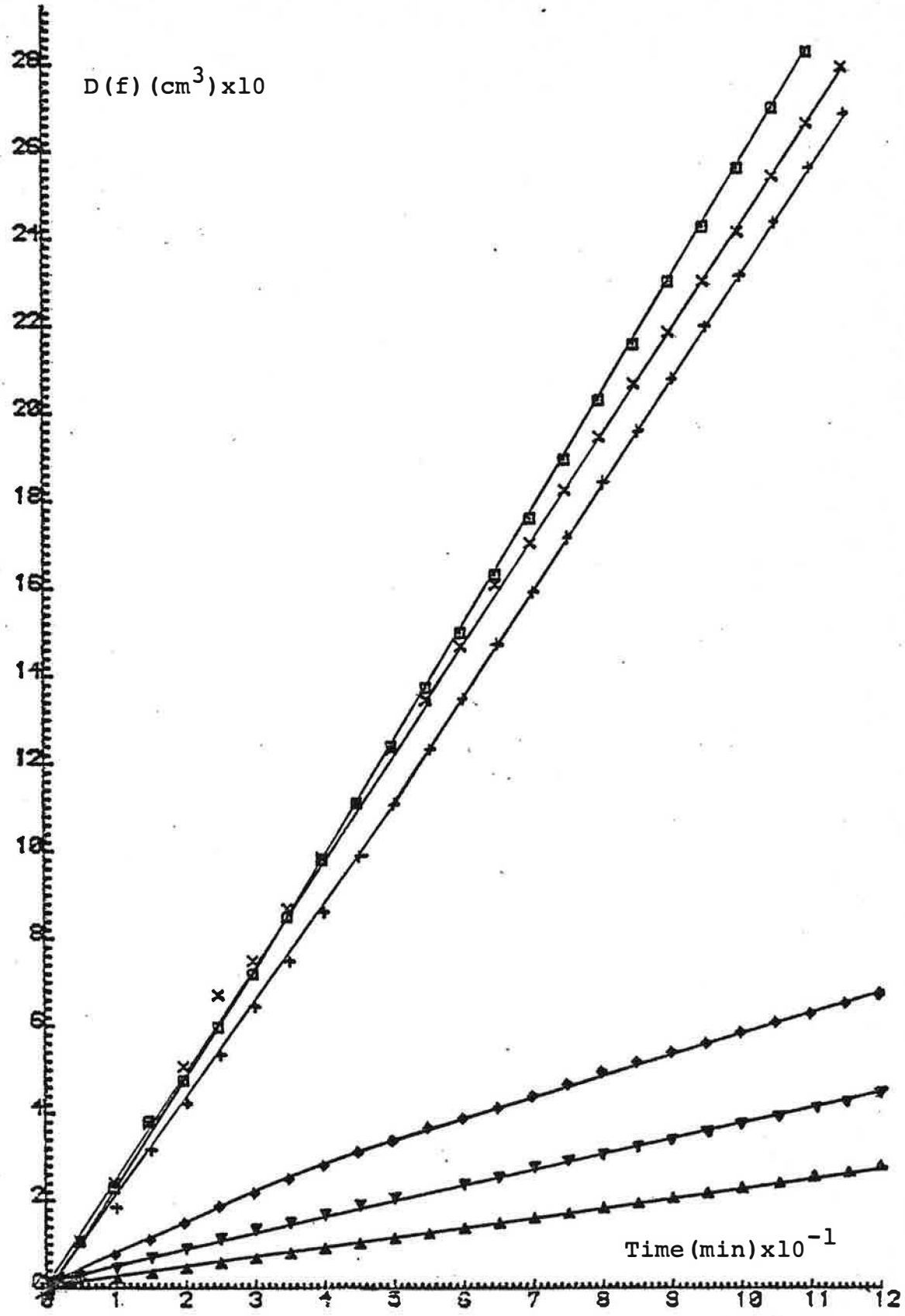


Figure 3.2. Effect of pH on salicylic acid release from Miglyol. (▲) pH 2.2, (▼) pH 3.0, (+) pH 5.0, (×) pH 7.0, (□) pH 8.0, (◆) distilled water.

Table 3.4. Effect of pH on salicylic acid release from salicylic acid/water and salicylic acid/ Miglyol solutions.

Donor solution	Receptor solution	Slope $cm^3\ min^{-1}$	Correlation coefficient	Degrees of freedom
D. water	D. water	0.0657	0.9999	12
	2.2	0.0604	1.000	16
	3.0	0.0565	0.9999	18
	5.0	0.0496	0.9998	16
	7.0	0.0480	0.9996	18
	8.0	0.0483	0.9994	13
Miglyol	D. water	0.0053	0.9967	21
	2.2	0.0023	1.0000	44
	3.0	0.0036	0.9987	44
	5.0	0.0236	0.9997	44
	7.0	0.0240	0.9999	44
	8.0	0.0261		44

barrier model, yielded gradually increasing transport constants and it has been suggested that ionized species possibly exaggerate the transfer of unionized species at elevated pH (Doluisio et al., 1964; Khordagy, Khalafallah and Khalol, 1981). On the other hand, Guy and Hadgraft (1981) reported that the interfacial transport of salicylic acid had no dependence on the acidity of the solution when unionized amount was taken into consideration. Since the partition coefficient is roughly the ratio of the solubilities of a drug in the oil and water phases, as a weak acid, aqueous solubility of salicylic acid increases with pH. Therefore, partition coefficient reduces and this results in increased release rates. In fact the partition coefficients of the drug between Miglyol and pH 2.2 and pH 8.0 buffer solutions were 27.28 and 0 respectively (Table 3.5).

As shown in Table 3.1, three emulsions with Cetamacrogol-1000, Cetamacrogol-1000 plus Cetostearyl alcohol (CSA) and Sodium Lauryl Sulphate (SLS) were prepared by the method given in 2.2.1 and the release experiments were conducted with distilled water and with pH = 2.2, 3.0, 5.0, 7.0 and 8.0 McIlvane buffer solutions as the receptor solutions. The release experiments were repeated for the control solutions containing the same amount of drug and the surfactants in water or Miglyol. Results are shown in Figures 3.3, 3.4 and 3.5 for Emulsion I-1, Figures 3.6, 3.7 and 3.8 for Emulsion I-2 and Figures 3.9, 3.10 and 3.11 for Emulsion I-3 respectively and the corresponding slopes calculated are summarized in Tables 3.6, 3.7 and 3.8.

Table 3.5. Apparent partition coefficients of salicylic acid with the absence and presence of surfactants, and the effect of the total amount of salicylic acid present in the system.

Total amount, g in 100 ml of the phases	Surfactant, g in 100 ml of the phases	K_{app}
0.0804	-	12.52
0.0824	-	15.42
0.0997	-	12.94
0.1018	-	13.52
0.1522	-	14.22
0.2012	-	15.31
0.1001 (pH=2.2)	-	27.28
0.1001 (pH=8.0)	-	0.00
0.1030	Cetomacrogol, 2.5	3.05
0.1066	Cetomacrogol, 3.0	3.41
0.1001 (pH=2.2)	Cetomacrogol, 3.0	3.72
0.0941	Cetomacrogol/CSA, 3.0/2.0	4.56
0.1001 (pH=2.2)	Cetomacrogol/CSA, 3.0/2.0	4.59
0.0949	NLS, 0.3	14.87
0.1001 (pH=2.2)	NLS, 0.3	20.39

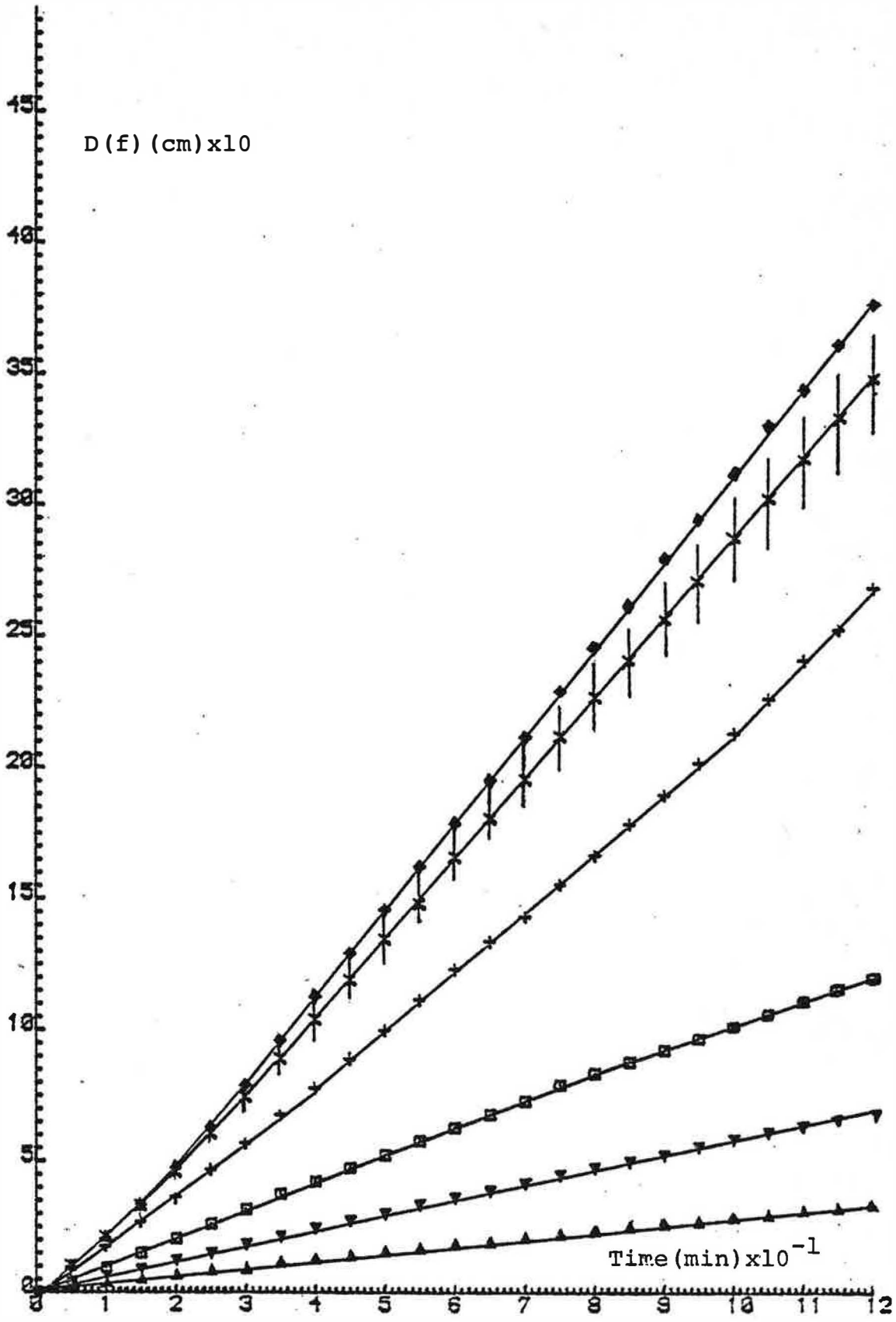


Figure 3.3. Effect of pH on salicylic acid release from Emulsion I-1. (▲) pH 2.2, (▼) pH 3.0, (+) pH 5.0, (×) pH 7.0, (◆) pH 8.0, (□) distilled water.

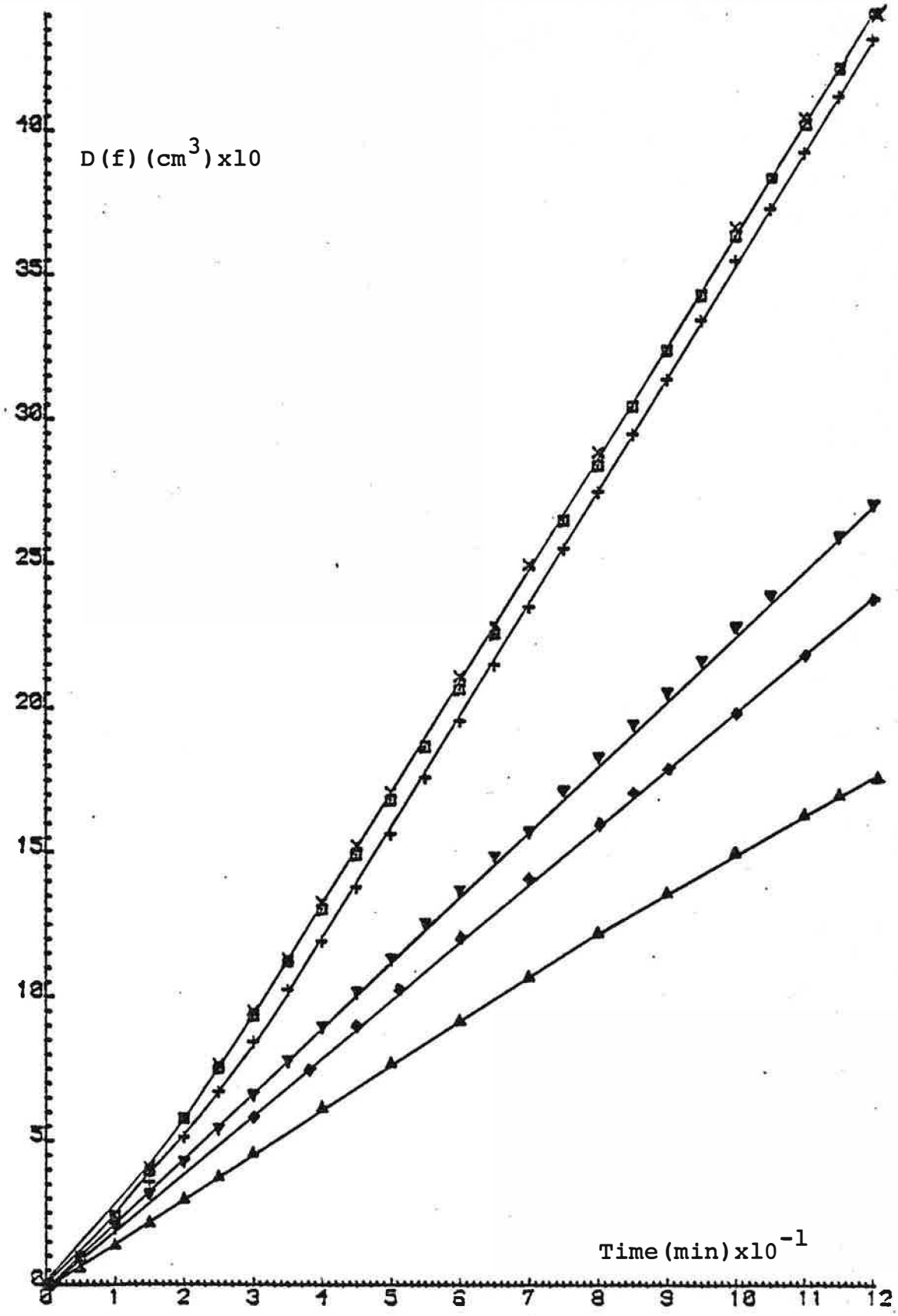


Figure 3.4. Effect of pH on salicylic acid release from aqueous cetomacrogol solution. (▲) pH 2.2, (▼) pH 3.0, (+) pH 5.0, (×) pH 7.0, (□) pH 8.0, (◆) distilled water.

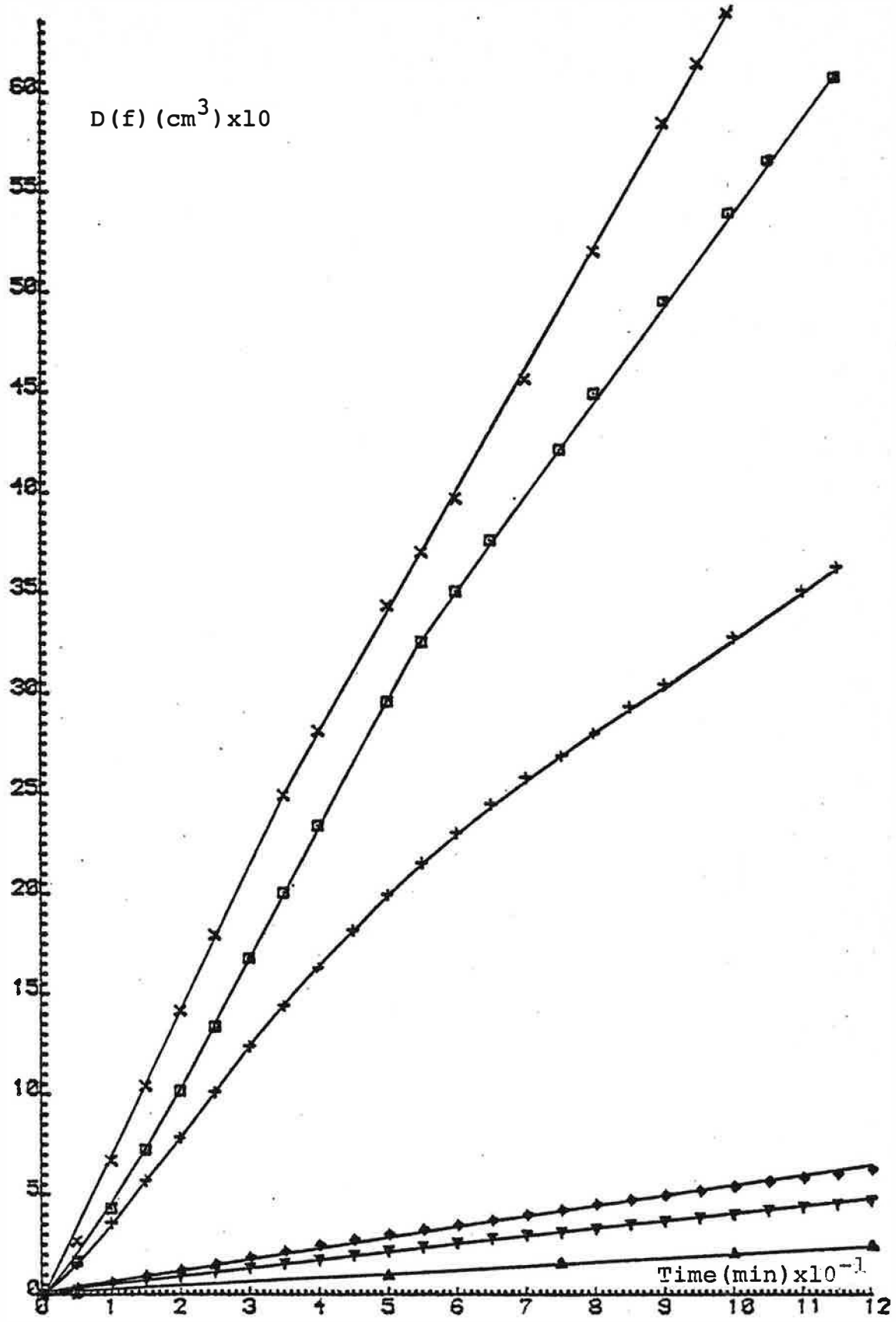


Figure 3.5. Effect of pH on salicylic acid release from cetomacrogol/Miglyol solution. (▲) pH 2.2, (▼) pH 3.0, (+) pH 5.0, (x) pH 7.0, (□) pH 8.0, (◆) distilled water.

Table 3.6. Salicylic acid release from Emulsion I-1, cetomacrogol/water and cetomacrogol/Miglyol solutions.

Donor	Receptor	Slope $cm^3\ min^{-1}$	Correlation coefficient	Degrees of freedom
Emulsion I-1	D. water	0.0104	0.9996	32
	2.2	0.0027	0.9977	44
	3.0	0.0057	0.9996	40
	5.0	0.0226	0.9991	44
	7.0	0.0297	0.9521	28
	8.0	0.0329	0.9999	16
Cetomacrogol/water	D. water	0.0199	0.9998	3
	2.2	0.0152	0.9998	10
	3.0	0.0229	0.9998	20
	5.0	0.0380	0.9994	21
	7.0	0.0383	0.9999	13
	8.0	0.0385	0.9998	15
Cetomacrogol/Miglyol	D. water	0.0051	0.9980	21
	2.2	0.0022	0.9997	21
	3.0	0.0038	0.9987	44
	5.0	0.0314	0.9899	15
	7.0	0.0636	0.9989	10
	8.0	0.0590	0.9982	11

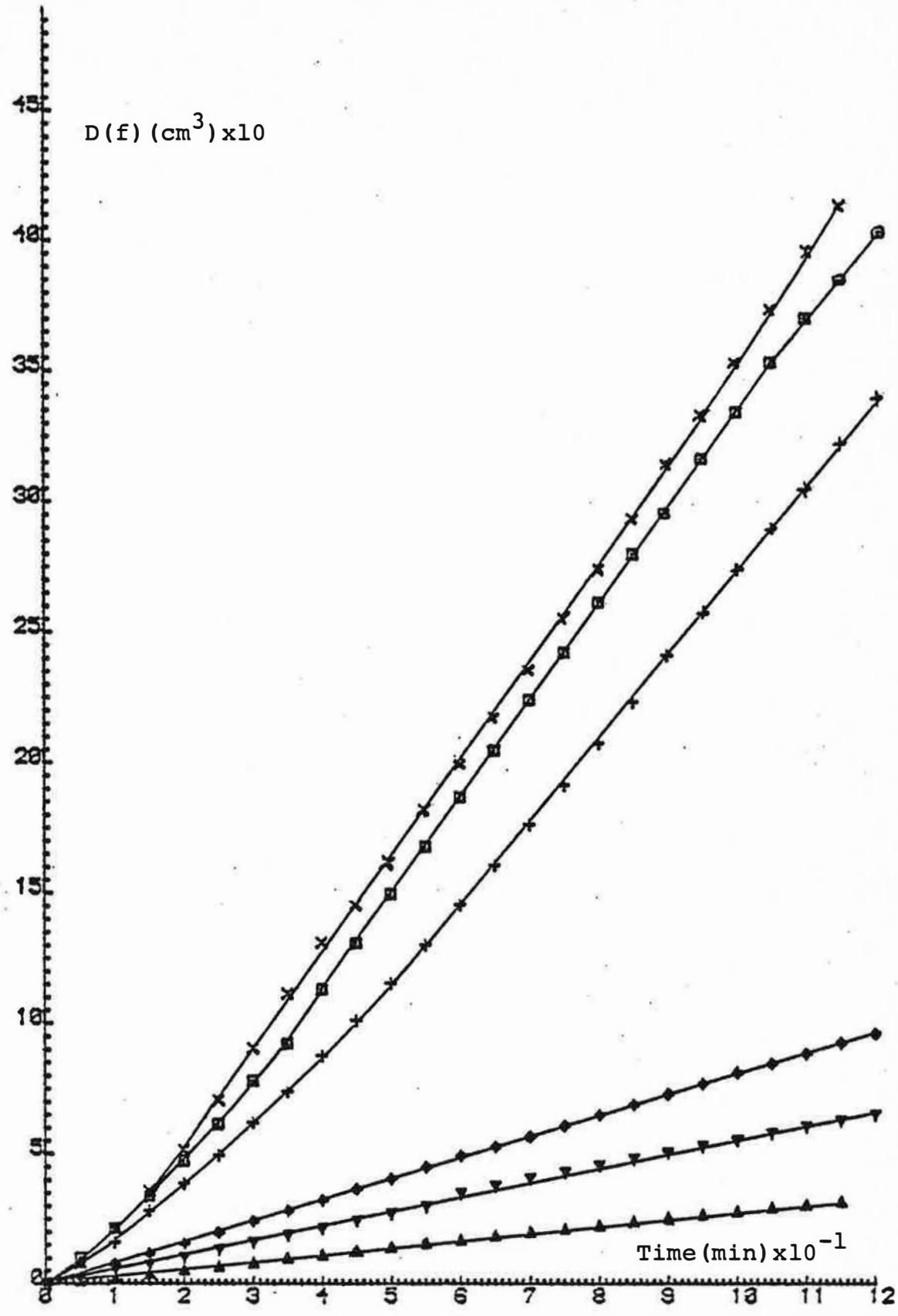


Figure 3.6. Effect of pH on salicylic acid release from Emulsion I-2. (▲) pH 2.2, (▼) pH 3.0, (+) pH 5.0, (x) pH 7.0, (□) pH 8.0, (◆) distilled water.

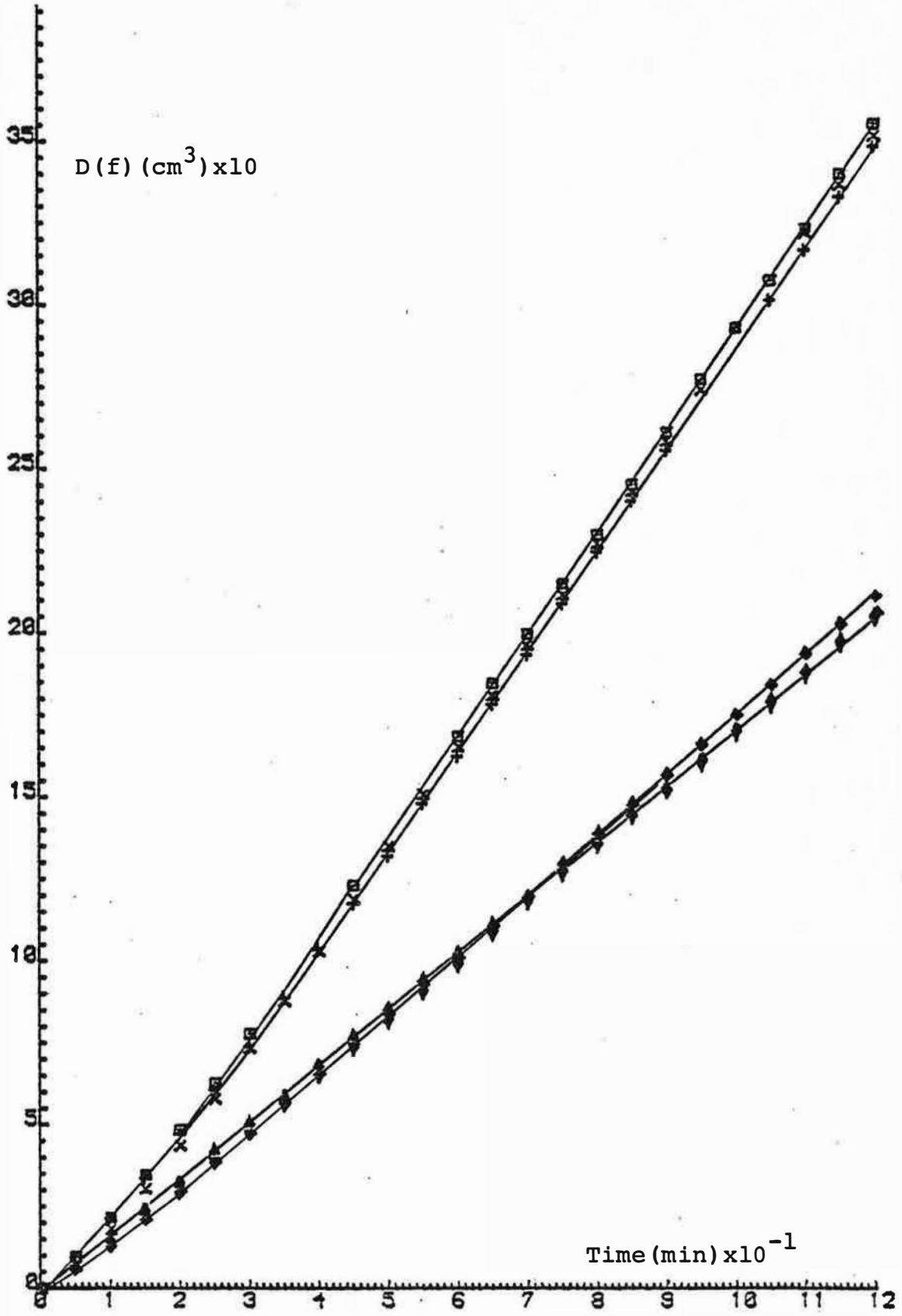


Figure 3.7. Effect of pH on salicylic acid release from cetomacrogol/CSA/water solution. (▲) pH 2.2, (▼) pH 3.0, (+) pH 5.0, (x) pH 7.0, (□) pH 8.0, (◆) distilled water.

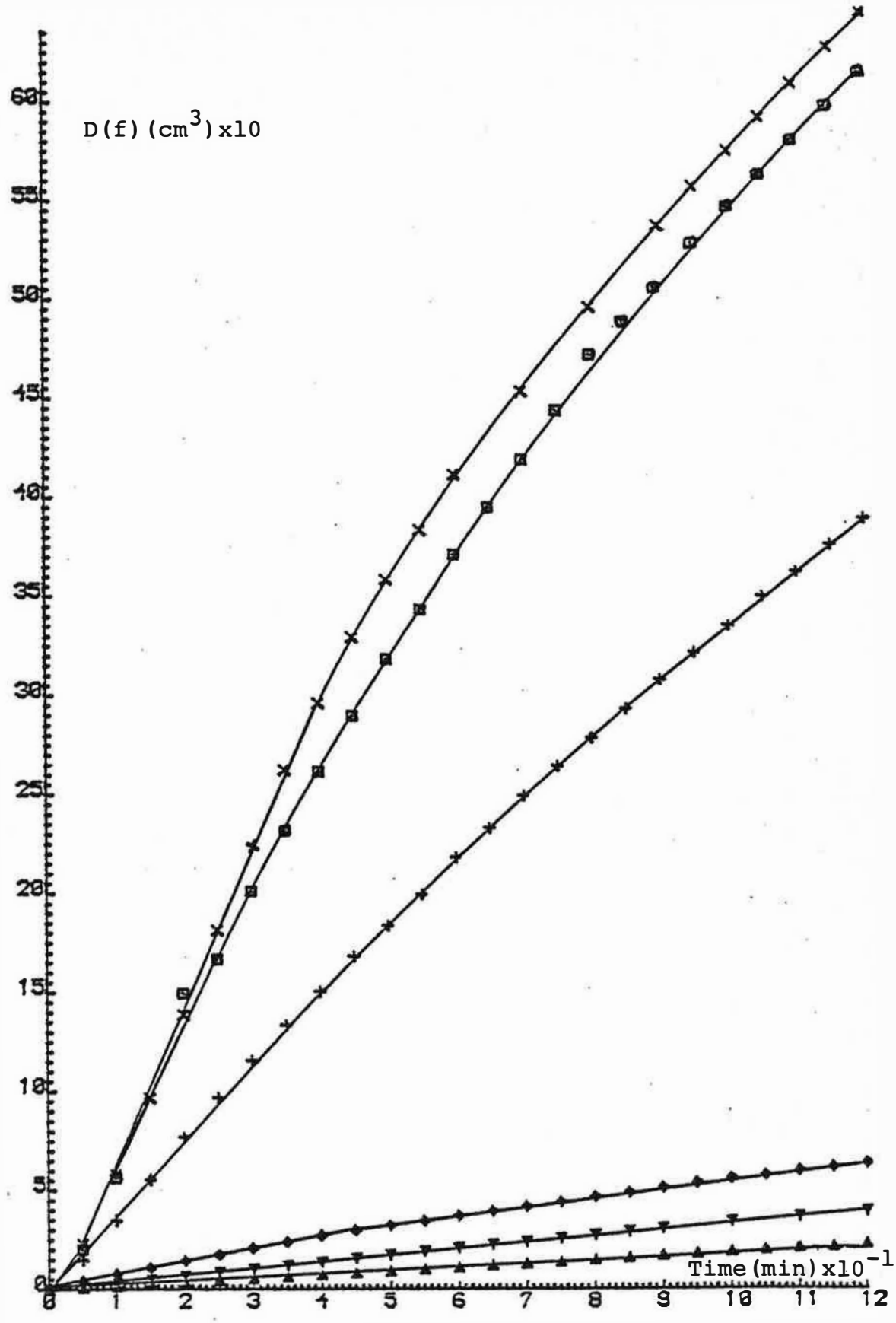


Figure 3.8. Effect of pH on salicylic acid release from cetomacrogol/CSA/Miglyol. (▲) pH 2.2, (▼) pH 3.0, (+) pH 5.0, (×) pH 7.0, (□) pH 8.0, (◆) distilled water.

Table 3.7. Effect of pH on salicylic acid release from Emulsion I-2, cetomacrogol/CSA/water and cetomacrogol/CSA/Miglyol.

Donor	Receptor	Slope $cm^3\ min^{-1}$	Correlation coefficient	Degrees of freedom
Emulsion I-2	D. water	0.0081	0.9999	21
	2.2	0.0028	0.9996	42
	3.0	0.0056	0.9987	67
	5.0	0.0281	0.9979	32
	7.0	0.0370	0.9999	36
	8.0	0.0363	0.9984	20
Cetomacrogol/CSA/ water	D. water	0.0181	1.0000	21
	2.2	0.0172	0.9614	32
	3.0	0.0174	0.9999	44
	5.0	0.0300	0.9997	40
	7.0	0.0307	0.9999	19
	8.0	0.0305	0.9999	17
Cetomacrogol/CSA/ Miglyol	D. water	0.0050	0.9964	21
	2.2	0.0019	0.9992	44
	3.0	0.0033	0.9991	38
	5.0	0.0317	0.9979	21
	7.0	0.0603	0.9881	11
	8.0	0.0567	0.9968	11

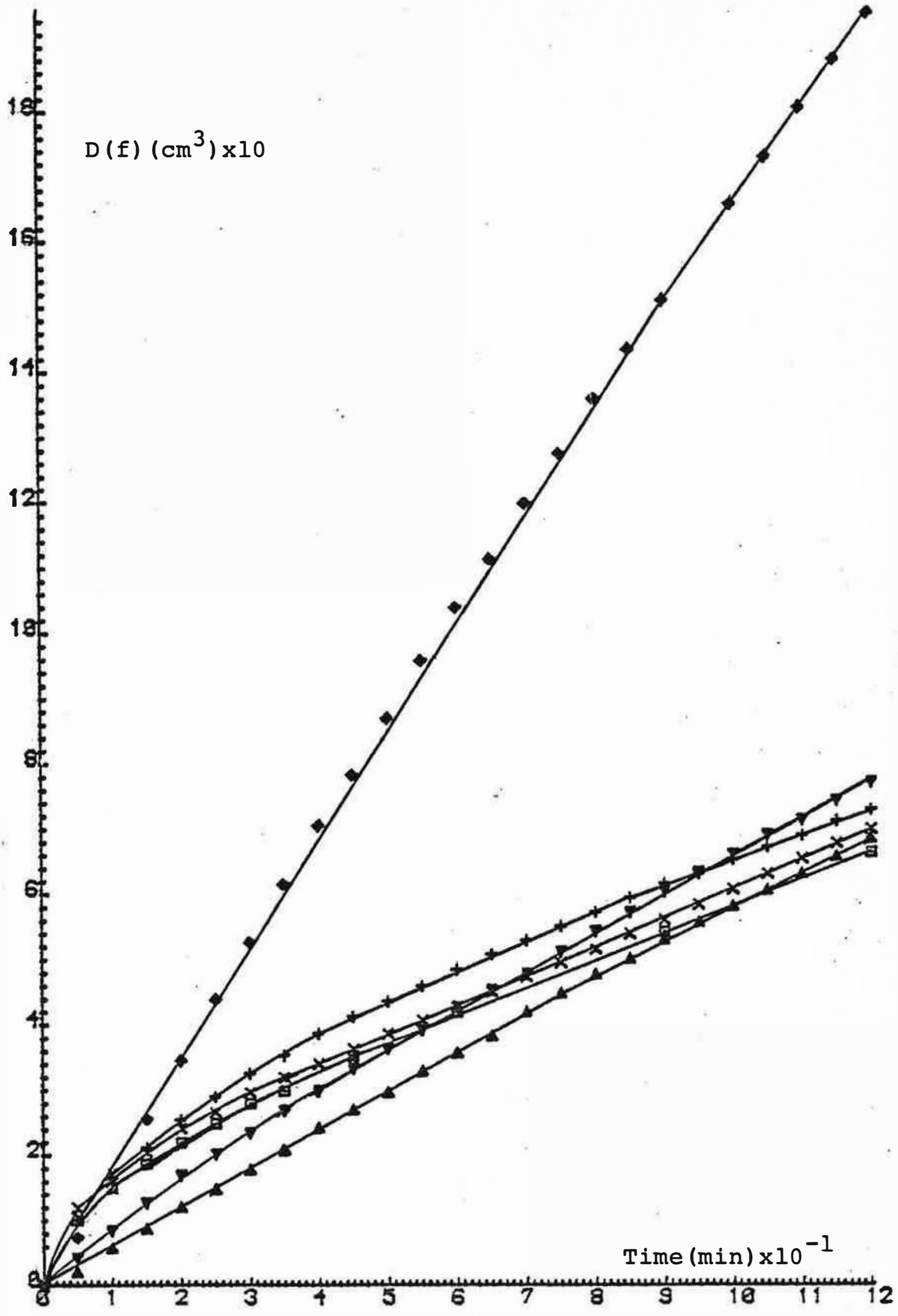


Figure 3.9. Effect of pH on salicylic acid release from Emulsion I-3. (▲) pH 2.2, (▼) pH 3.0, (+) pH 5.0, (×) pH 7.0, (□) pH 8.0, (◆) distilled water.

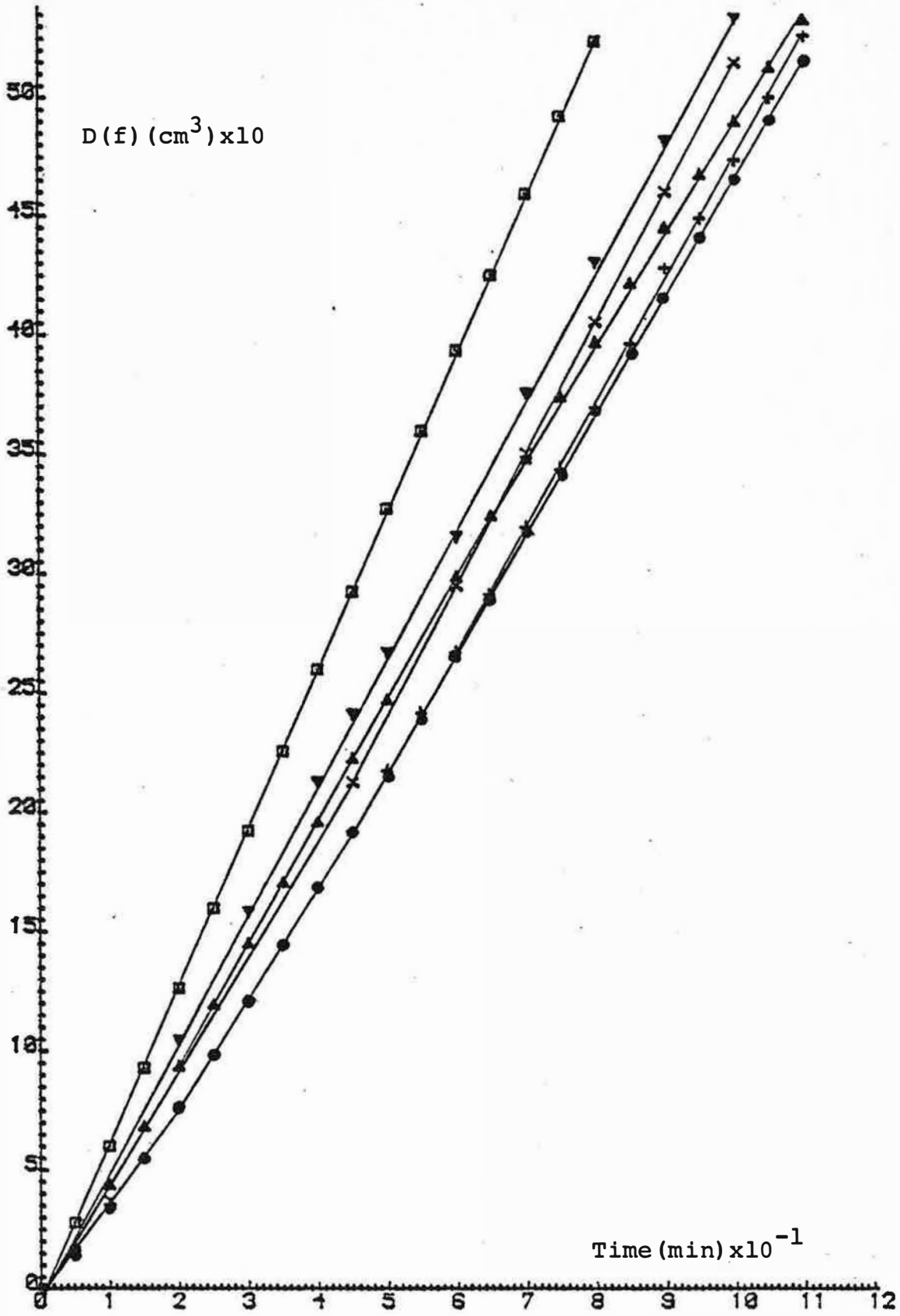


Figure 3.10. Effect of pH on salicylic acid release from SLS/water solution. (▲) pH 2.2, (▼) pH 3.0, (x) pH 5.0, (+) pH 7.0, (□) pH 8.0, (◆) distilled water.

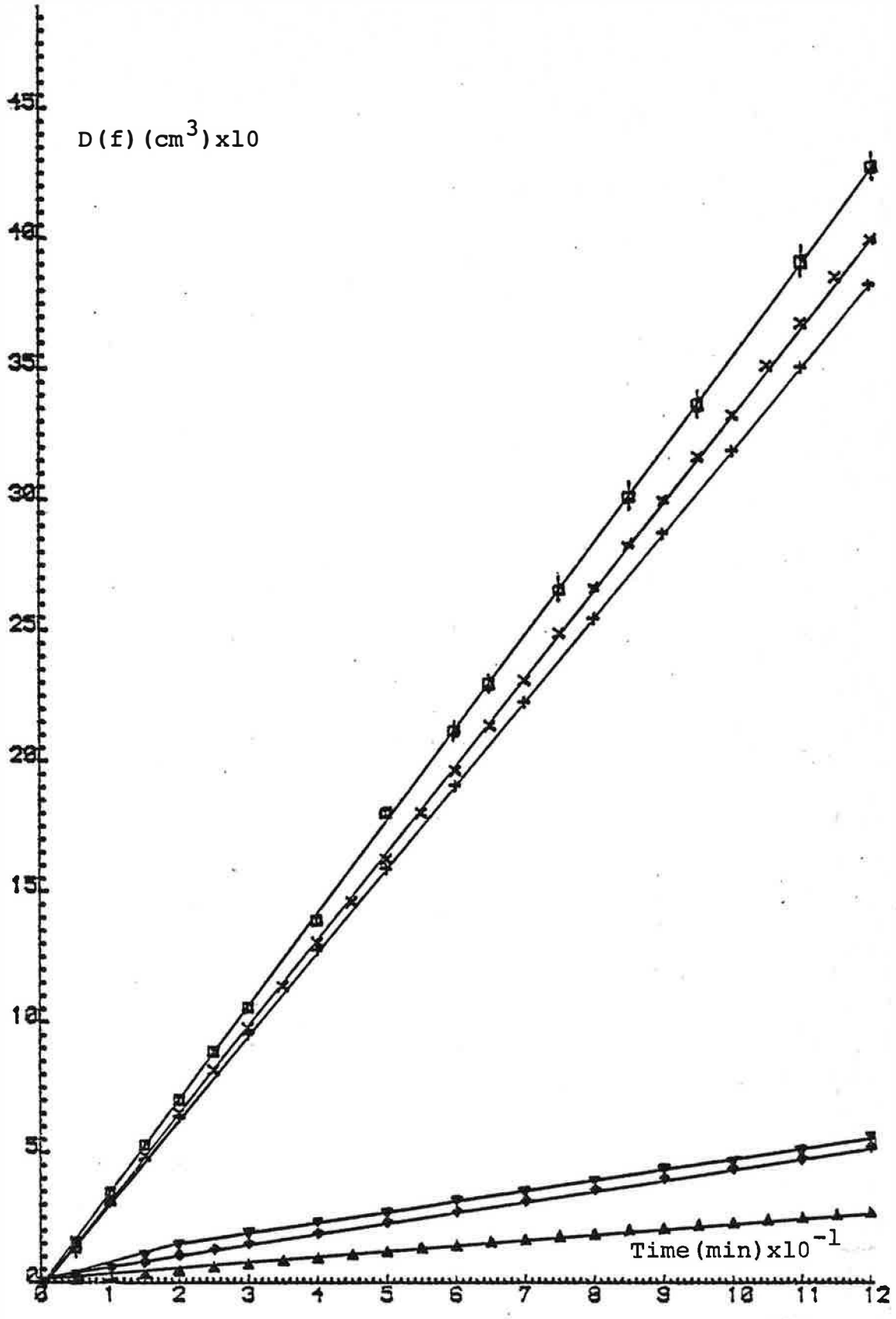


Figure 3.11. Effect of pH on salicylic acid release from SLS/Miglyol solution. (▲) pH 2.2, (▼) pH 3.0, (+) pH 5.0, (×) pH 7.0, (□) pH 8.0, (◆) distilled water.

Table 3.8. Effect of pH on salicylic acid release from Emulsion I-3, NLS/water and NLS/Miglyol solutions.

Donor	Receptor	Slope $cm^3\ min^{-1}$	Correlation coefficient	Degrees of freedom
Emulsion I-3	D. water	0.0162	0.9993	42
	2.2	0.0057	0.9995	44
	3.0	0.0061	0.9991	44
	5.0	0.0080	0.9961/0.9990	12/28
	7.0	0.0085	0.9909/0.9999	4/36
	8.0	0.0065	0.9925/0.9993	12/8
NLS/water	D. water	0.0662	1.000	32
	2.2	0.0494	0.9997	38
	3.0	0.0532	0.9998	20
	5.0	0.0516	0.9997	14
	7.0	0.0497	0.9996	34
	8.0	0.0490	0.9998	14
NLS/Miglyol	D. water	0.0046	0.9997	26
	2.2	0.0023	0.9992	44
	3.0	0.0051	0.9999	6
	5.0	0.0319	1.000	22
	7.0	0.0336	0.9999	36
	8.0	0.0349	0.9994	40

In order to compare the release rates of the three emulsions and the control solutions with the release from water and Miglyol, the slopes in Tables 3.6, 3.7 and 3.8 were plotted against pH (Figure 3.12). Except for Emulsion I-3, the release from Miglyol was the slowest of all at every pH value. This could be attributed to the slower diffusion coefficient of the drug in the more viscous oil. Therefore, the rate limiting step could be the release from the oil phase.

When surfactants were incorporated in the oil phase the release was enhanced, especially at high pH values. Waggoner et al. (1971) have also reported higher release rates from oily surfactant solutions than from oil alone stating that the surfactants did not hinder the release. However, current experiments have indicated that the faster release rates were due to an emulsion layer formed at the bottom of the donor cell. In the presence of the surfactants, the interfacial tension between the donor solution and the water filling the pores of the membrane was lowered and a layer of an o/w emulsion was formed in situ. Thus, the observed salicylic acid release was from this emulsion layer and not from the oily surfactant solution. Furthermore, when the pH of the external phase of this emulsion formed in situ was high, the release rate was faster due to an increased concentration of salicylic acid in the emulsion. Although the slopes were included in Figure 3.12 corresponding to the oily surfactant solutions, they cannot be related to the effect of the surfactants on drug release from the oily solutions.

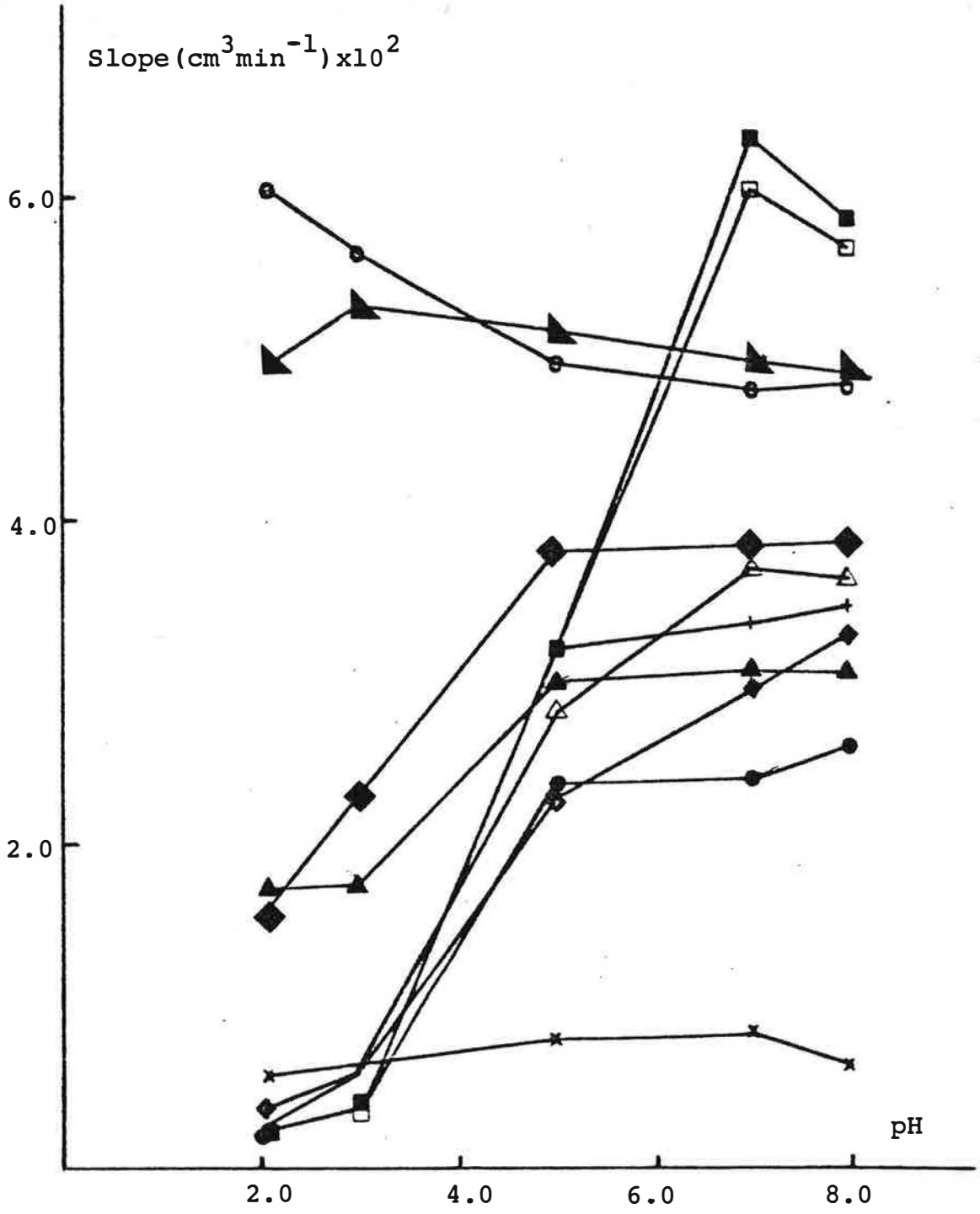


Figure 3.12. Effect of pH on salicylic acid release from the emulsions and control solutions. (○) Aqueous solution, (●) oily solution, (◆) Emulsion I-1, (◆) cetomacrogol/water, (■) cetomacrogol/Miglyol, (△) Emulsion I-2, (▲) cetomacrogol/CSA/water, (□) cetomacrogol/CSA/Miglyol, (×) Emulsion I-3, (◣) SLS/water, (+) SLS/Miglyol.

Release from the aqueous salicylic acid solution was the highest at every pH value since there was no partitioning step or interface between the donor and the receptor solutions. Depending upon the pH, unionized or unionized/ ionized salicylic acid molecules diffused in water, therefore the apparent diffusion coefficient of salicylic acid was important. However, when surfactants were added to the aqueous solution, release was slower at every pH value than that of pure aqueous solution. This was due to micelle formation and solubilization of salicylic acid in the micelles reducing the amount of the drug available for release. Since the amount of SLS was just above the CMC, which is 2.49 g/l (Shinoda et al., 1963), the solubilization was not significant in SLS micelles resulting in similar release rates to simple aqueous solution especially at higher pH.

Release of the drug from Cetomacrogol/CSA mixed micelles was slower than that from the other micelles at every pH due to their larger size (Harkins, Matton and Mittelmann, 1947) which increases the amount of the drug entrapped. Also, the closer packing of the Cetomacrogol and CSA molecules would further decrease the release of the drug solubilized in these mixed micelles compared with the release from the simple Cetomacrogol micelles. The effect of the pH on the drug release from these micellar solutions was again as expected obeying the pH-partitioning rule that the release rate increased with increasing pH (Figure 3.12). Similarly, emulsions, except for Emulsion I-3, released the drug faster when pH was increased due to the change in the apparent partition coefficient of the drug. Several workers have

reported that the release rate is inversely proportional to the partition coefficient (Bean, Konning and Thomas, 1970; Schumacher, 1971 a and b; Kakemi et al., 1972 a and b; Koizumi et al., 1968 a and b; Windheuser et al., 1970).

Drug release from the emulsions was not significantly different from that of the oily solution at lower pH values possibly suggesting the existence of an interfacial barrier in the emulsion. Because of emulsification of the oil, the effective surface area available for the diffusion of the drug was significantly higher in emulsions than the area of the membrane which roughly represented the effective area for diffusion from the oil itself, and this should have had an increasing effect on the release from all of the emulsions. Similarly, the differences in the release characteristics of the emulsions, which were prepared to have the same oil/water ratio, further suggested that this was due to the different interfacial films which acted as different barriers to the release of the drug from the oil globules of the emulsions. However, the faster release from Emulsion I-2 than Emulsion I-1 was not expected. As shown in Figure 3.13 and Table 3.2, Emulsion I-2 was more viscous than Emulsion I-1 due to the self-bodying action of surfactant/fatty alcohol complex (Barry, 1969; Talman and Rowan, 1970). The Cetomagrogol/CSA complex was also expected to form a stronger interfacial film (Halworth and Carless, 1973) on the oil globules of Emulsion I-2. Release is inversely proportional to the viscosity (Levy and Jusko, 1965; Windsheuser et al., 1970; Flynn et al., 1974) and the complex interfacial film should act as a stronger barrier to release, therefore Emulsion I-2

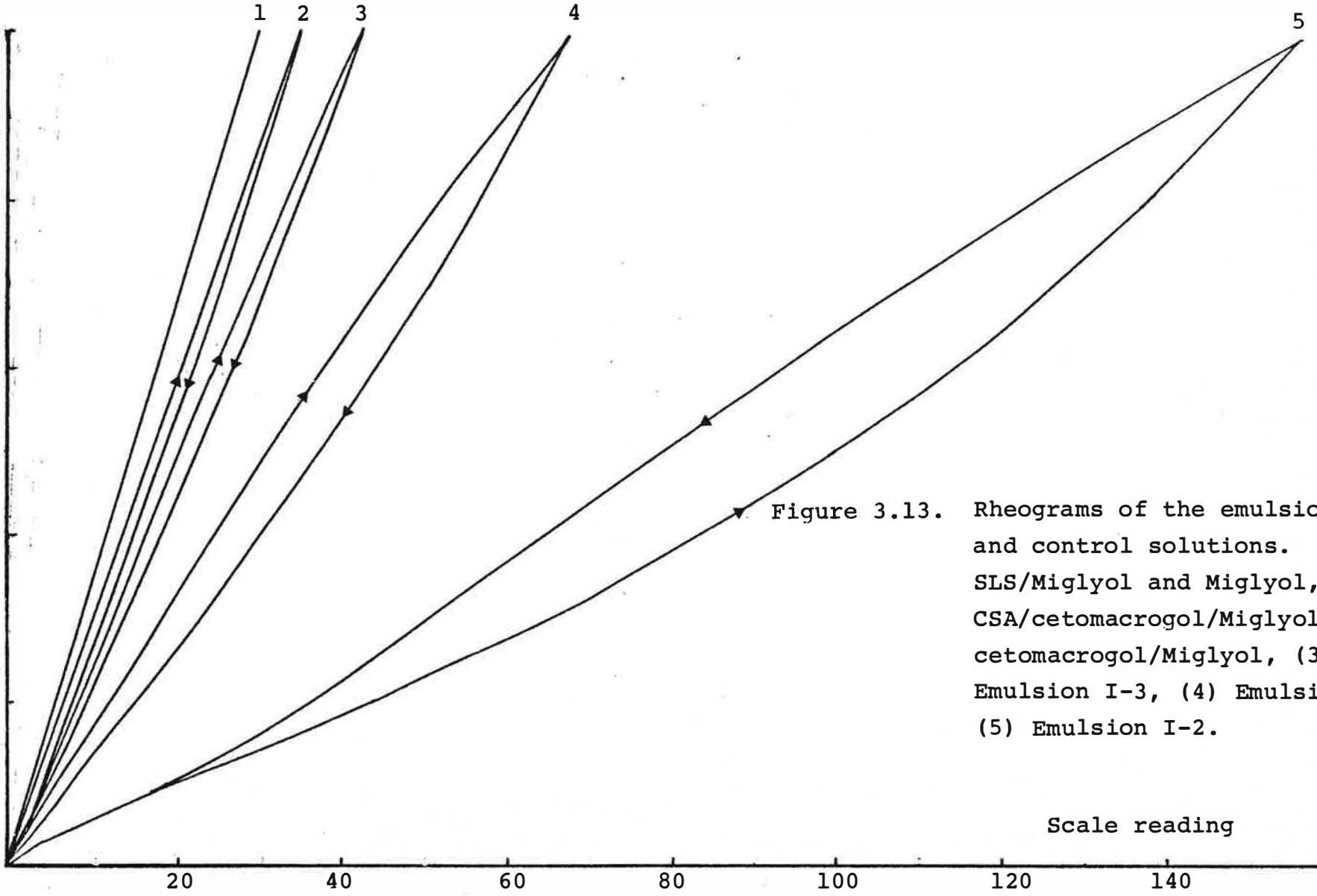


Figure 3.13. Rheograms of the emulsions and control solutions. (1) SLS/Miglyol and Miglyol, (2) CSA/cetomacrogol/Miglyol and cetomacrogol/Miglyol, (3) Emulsion I-3, (4) Emulsion I-1, (5) Emulsion I-2.

* Cone speed (rpm) is 100 for 1 and 2, and 1000 for 3, 4 and 5.

should have released the drug slower than Emulsion I-1. The results reported in Figure 3.12 indicated that either the interfacial barrier was a weaker barrier than the film formed by Cetomacrogol alone or there were some other variables affecting the drug release. The particle size distribution appeared to differ in some way as shown in Table 3.9. Although this was considered as an important factor on drug release (Higuchi, 1964; Surpuriya et al., 1972 a and b; Yotsuyanagi et al., 1973) due to the increased surface area available to release, the higher release rate observed here could not be attributed to this. It was felt that more information was needed to explain the mechanism of the release from emulsions and to define the possible variables affecting it.

In the case of Emulsion I-3, increasing pH had a different effect as shown in Figure 3.12, probably due to a change in the interfacial film. Although the slopes which were stated in Table 3.8 and Figure 3.12 were the slopes of the lines fitted between 20 and 120 minutes with high correlation coefficients, Figure 3.9 shows the biphasic character of the release at higher pH values of 5.0, 7.0 and 8.0 supporting the hypothesis of a change in the interfacial barrier. This change was probably due to a complex film formation on the globules by SLS and lauryl alcohol which was a hydrolysis product of SLS at high pH, and this resulted in a change in the release properties of the emulsion. However, the ability of the lauryl alcohol to block the pores of the membrane was also considered, but the same problem was not seen when the control solutions were tested.

Table 3.9 . Particle size distribution of the emulsions, percent droplets in each size interval.

Diameter in µm	< 1	1-2	2-3	3-4	4-5	5-6	6-8	8-10	> 10
Emulsion I-1	59.72	34.19	4.03	0.98	0.74	0.25	-	-	-
Emulsion I-2	81.64	15.79	1.40	0.94	0.23	-	-	-	-
Emulsion I-3	76.81	18.94		3.10	1.02	-	-	0.18	

Therefore, the biphasic character of the release from Emulsion I-3 was attributed simply to the hydrolysis of SLS and a formation of a new coherent film on the globules (Halworth et al., 1972; Schulman et al., 1940).

3.5 Conclusion

As discussed in section 3.4, the drug release from the emulsions was never as fast as the release from the aqueous solution, but it was faster than that from the oily solution. This could be attributed to the phase volume ratio that the drug in oil and water represented $\phi=\infty$ and $\phi=0$ respectively and the emulsions were between these two. On the other hand, the different release properties of the emulsions having the same phase volume ratio did indicate the existence of different interfacial films on the globules and the possibility of this being an important variable affecting the release from emulsified systems. The results reported in this chapter did not provide any information as to whether there was any contribution of the micellar phase of the emulsion to the overall release, although the aqueous micellar solutions did affect the release when compared with the simple aqueous solution.

In conclusion, although it was shown that with different emulsion formulations the overall release of a drug could be changed, more information is needed to explain both the mechanism of drug release from emulsions and the variables affecting it. Therefore, it was decided that the effect of

(1) the surfactant type and concentration,

(2) the oil/water volume ratio,

(3) the micellar phase of the emulsion,

(4) the apparent and true partition coefficients,

(5) the particle size distribution, and

(6) the ageing on drug release from emulsions

should be studied in more detail to characterize the variables which control or affect the release properties of the emulsions.

CHAPTER 4

TERNARY PHASE DIAGRAMS

4.1 Introduction

A general introduction and the pharmaceutical importance of producing phase diagrams have been considered in Chapter 1 (1.5). In this chapter the objective was the study of the formation of stable emulsions, with and without mesophases, appropriate for use in drug release experiments. These studies consisted of investigations of the phase equilibria between Miglyol, water and surfactants at 25°C, where sodium lauryl sulphate, cetrimide and cetomacrogol-1000 represented anionic, cationic and non-ionic surfactants respectively.

4.2 Experimental

As given in 2.2.8, the mixtures were prepared in identical screw-capped glass-vials, then placed in a shaking water bath at 70°C for at least 3 hours and mixed thoroughly with a whirlmixer or a glass rod. The vials were then kept in an incubator at least for a week at 25°C to ensure equilibrium to be reached. Some of the thick samples were checked again after 4 weeks.

The terms L_1, L_2 , LC and S represent aqueous phase, oily phase, liquid crystal and solid phases respectively. When there were two or more phases, combined terms were used, such as L_1+L_2+LC etc. Phase changes and the state of equilibrium were determined both visually and microscopically. The single isotropic liquids were clear with low viscosity

and showed no birefringence. Systems containing two isotropic liquid phases, viz. emulsions, were turbid or milky on shaking, with low viscosity and no birefringence. In the liquid crystalline phases, appearance of slimy viscoelastic masses to high viscosity textures indicated the likely presence of mesomorphic phases on a macroscopic scale. The polarizing microscope was used to confirm the presence of mesophases and their structure. The solid in all cases was the surfactant used and the characteristic crystalline structure of the pure state was used to indicate its presence. Photomicrographs of the mesophases were taken to compare them with the published data (Rosevear, 1968; Ekwall, 1975) and to identify the type of phase. The emulsion type was determined by observing the spread of the emulsion between the slide and the cover slip when a drop of water was added. The o/w emulsions found have spread easily upon the addition of water, while w/o emulsions would not have spread.

Two or three phase mixtures can possibly be in equilibrium, especially near the boundaries drawn in the diagrams. No attempt, however, was made to separate these by any other means, such as centrifugation. The spontaneous separation of the phases and microscopic examination were only taken into account to draw the boundaries on the diagrams. Therefore, the boundaries were drawn with maximum error of ±2.5% of the concentrations of the components.

4.3 Results and discussion

4.3.1 Ternary diagram of Miglyol/water/cetomacrogol-1000

The phase diagram obtained with oil/water/non-ionic

surfactant is shown in Figure 4.1. The phases identified are L_1, L_2, middle (E) and isotropic viscous gel phase (I). The emulsions observed were all o/w emulsions and were stable; although there was creaming, no visible oil separation was observed. Increasing both the oil and cetomagrocol concentrations increased the viscosity of these emulsions.

On the surfactant-water axis the L_1 solution started to form a gel above about 25% surfactant which became rather hard and stiff with further increasing concentrations of surfactant. As can be seen from Figure 4.1. this gel occupied a large area on the diagram between L_1 and L_2 micellar solution regions. This rigid and transparent gel is characterized by its isotropic nature, explicable by its cubic structure resulting from the close packing of spherical micelles into a body-centered cubic arrangement (Lo et al., 1977; Lachampt, 1967; Ekwall, 1975). It has been inferred that some I phases are of the normal type, being composed of amphiphile aggregations having a hydrocarbon core with the hydrated polar groups directed outwards from it (type I_1), while others are of the reversed type, composed of aggregations having a core of hydrated polar groups with the hydrocarbon parts directed outwards (type I_2). The normal type (I_1) is generally in the zone between mesophases E and D and between E and solution region L_1 or L_2, or it can be in equilibrium with E and D or with L_1 and L_2 (Ekwall, 1975). Both types of isotropic viscous gel phases were observed and are shown in Figure 1 between L_1, L_2 and mesophases of normal and reversed middle types. Similarly, the existence of I_1 and

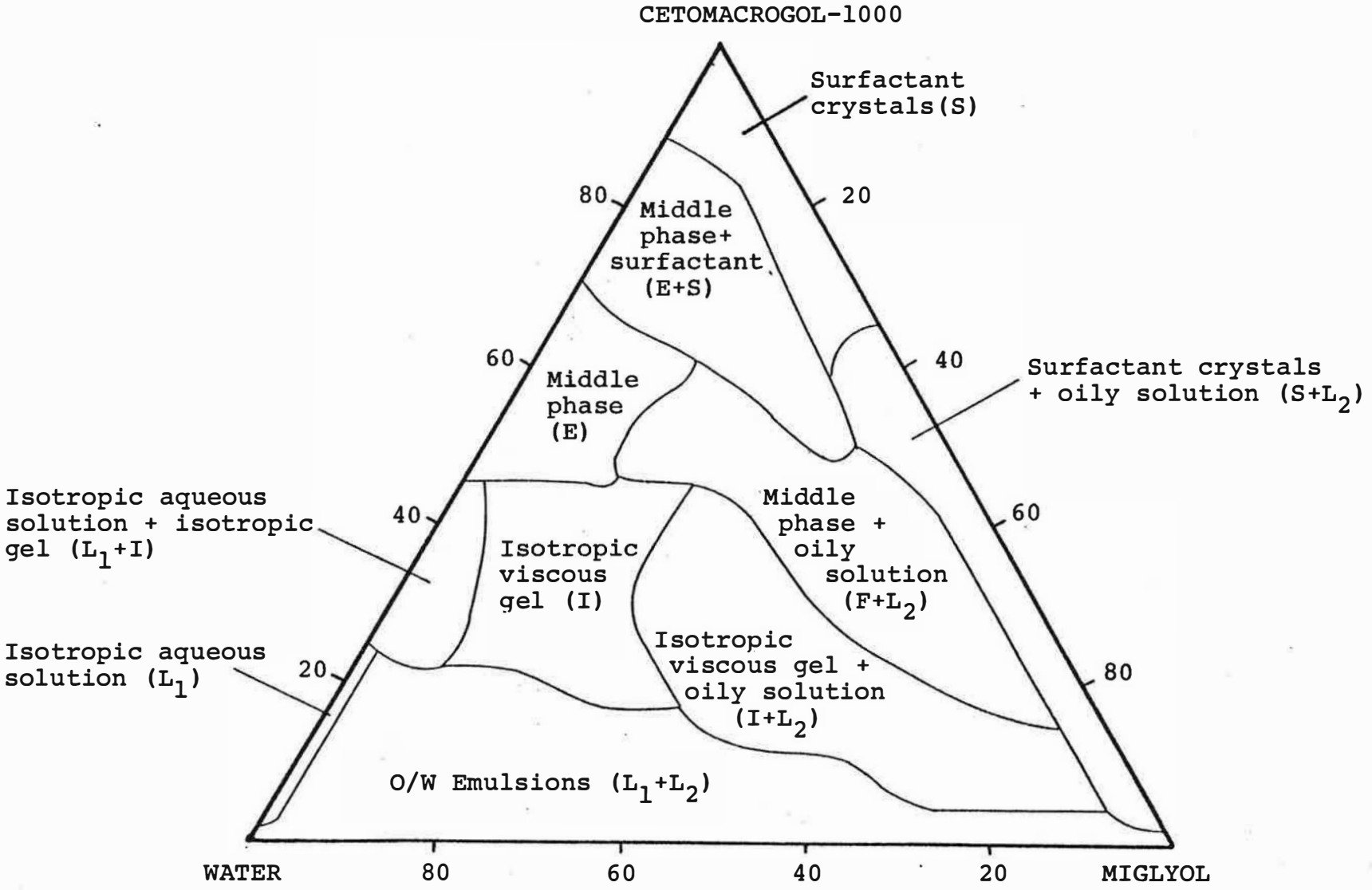


Figure 4.1. Ternary phase diagram of water/Miglyol/cetomacrogol at 25°C.

I_2 isotropic gel phases has been reported for ternary systems of other non-ionic surfactants as well as ionic ones (Ekwall, 1975; Ekwall et al., 1969; Lachampt, 1967; Lo et al., 1977; Adrangui et al., 1979).

The only anisotropic phase observed was middle phase. It is possible that the ethoxylated chain hinders the equidistant sheet structure formation in the presence of water, thus neat phase is not formed (Lachampt, 1967; Winsor, 1968). Winsor (1968) has discussed the factors controlling the formation of middle and neat phases. He found that in a non-ionic series the bulky polar groups of long chain ethylene oxide condensates are predisposed to middle phase formation, while short chain compounds form neat phases. This has been confirmed by Lachampt (1967), Ekwall et al. (1969) and Lo et al. (1977) and the present results also supported Winsor's observations. On the contrary, using Tween and Span blends, Al-Mamun (1977) found neat phases to be formed, while Adrangui et al. (1979) have reported both middle and neat phases. As shown in Figure 4.1, middle phase was observed between the isotropic gel (I) and the oily solution and the solid surfactant-L_2 regions. Like I phase, the middle phase is a stiff, viscous and a fairly transparent gel which is anisotropic; under the microscope between polaroid plates it displays a fan-like or angular texture. Middle phase has a two-dimensional hexagonal structure consisting of parallel amphiphilic rods in hexagonal array. The rods are considered to be composed of more or less radially disposed molecules of amphiphile having the hydrocarbon parts directed inwards and the hydrated polar

groups facing outwards (the normal type, E) or with the polar groups directed inwards and the hydrocarbon parts directed outwards (the inverse type, F). In the ternary diagram of Miglyol-water-cetomacrogol both types of middle phases were observed (Figure 4.1). With higher surfactant concentrations, the middle phase was in equilibrium with the pure cetomacrogol crystals.

With the concentrations of the three substances studied, a pure oily micellar solution (L_2) region was not observed due to the low solubility of cetomacrogol in Miglyol. Pure cetomacrogol crystals were dispersed in oil forming a white, soft semi-solid to hard waxy solid mixture on the oil-surfactant axis.

Up to 10% of the surfactant concentration, more samples were prepared with 0.5% increments of the surfactant concentrations. The emulsions obtained were all o/w type and stable.

4.3.2 Ternary phase diagram of water/Miglyol/sodium lauryl sulphate (SLS)

As shown in Figure 4.2, neat phase (D) was the dominating mesophase observed in this ternary diagram and it was generally in equilibrium with the other phases such as emulsions (L_1+L_2), oily solution, surfactant crystals or middle phase (E). This phase displayed a semi-liquid and gel-like consistency throughout all regions of existence regardless of composition, but the overall appearance and viscosity of the whole system changed with the composition from fluid emulsion to rather thick semi-solid cream. Microscopic examination between crossed polaroids showed

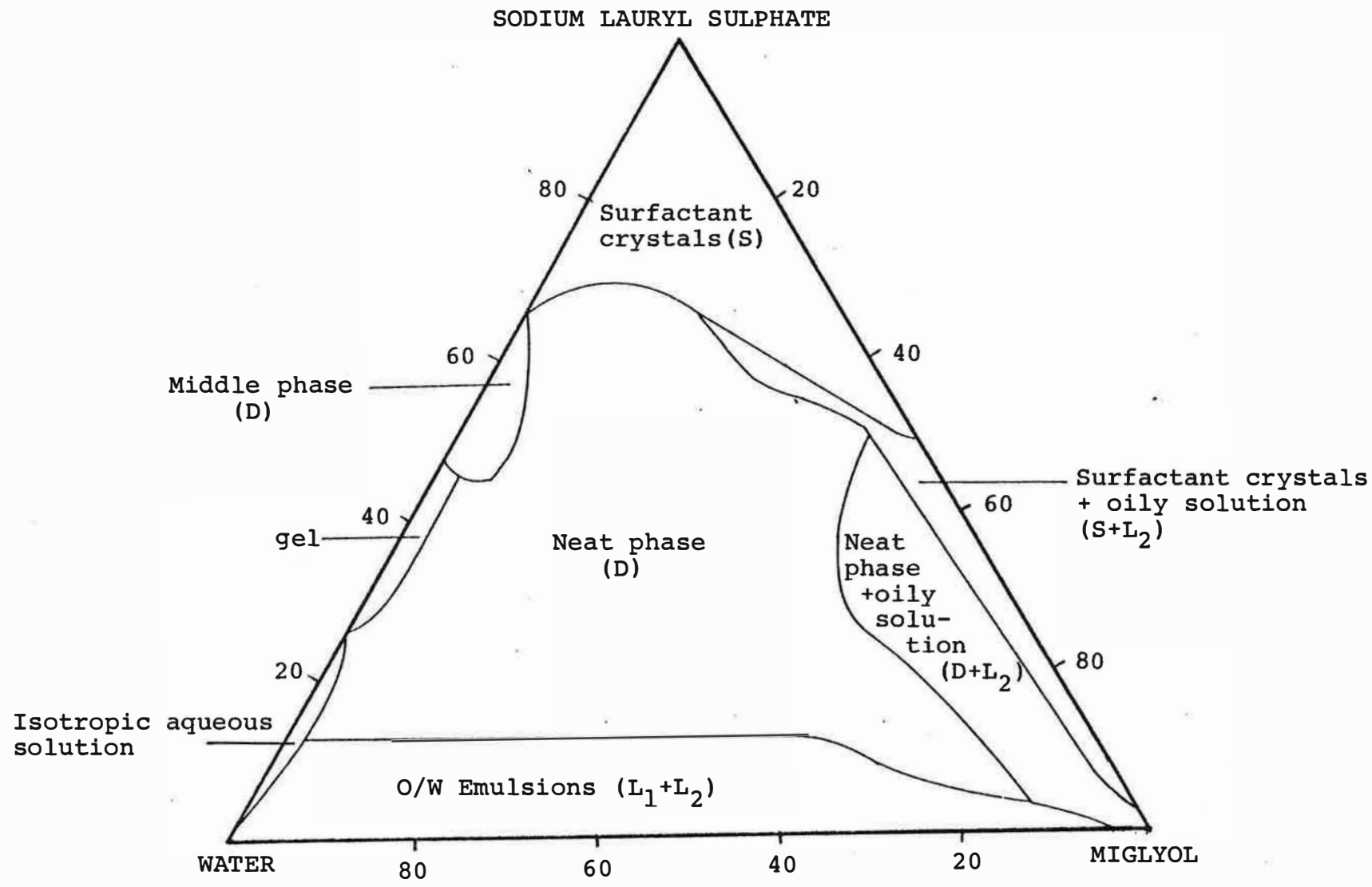


Figure 4.2. Ternary phase diagram of water/Miglyol/sodium lauryl sulphate at 25°C.

both mosaic and planar textures, as well as in some cases numerous spherical and mostly optically positive units were observed.

X-ray diffraction studies have revealed that the neat phase has a lamellar structure with layers of amphiphile molecules oriented with the hydrocarbon chains together and the polar groups in the boundaries with layers of water (Fontell et al., 1962; Husson et al., 1960). This phase may be in equilibrium with isotropic solutions ($D \rightleftharpoons L_1$; $D \rightleftharpoons L_2$) or with various other mesophases (Ekwall, 1975).

On the water-surfactant axis, the L_1 solution became turbid due to the hydrolysis of SLS with time and above about 25% surfactant there was a semi-solid anisotropic gelled region. This phase appeared in the form of narrow, spindle-shaped crystals under both visible and polarized light. When the concentration of SLS further increased, the gel became more viscous and displayed the striated texture of a middle phase (Figure 4.2). This transformation is due to the increasing anisometry of the micelles that results from the crowding in the solution (Ekwall, 1975). The upper limit of the middle phase observed was in equilibrium with the soap crystals. On the other hand, with the additions of oil, the middle phase became equilibrated with the lamellar phase, neat phase (D), which extended till L_2+soap crystals region (Figure 4.2).

Pure L_2 region was again not observed and was always in equilibrium with other phases. The stiff and viscous isotropic gels (I) observed with water/Miglyol/cetomacrogol did not appear in this ternary system.

The o/w emulsions were stable and no oil separation was observed over a period of three months.

4.3.3 Ternary phase diagram of water/Miglyol/cetrimide (CTAB)

As shown in Figure 4.3, the mesophases observed in this ternary diagram were similar to that of the water/Miglyol/SLS ternary systems, however the middle phase and the middle + neat phase regions occupied larger areas. The isotropic viscous gel (I) again did not appear in this ternary system.

Increasing surfactant and oil concentrations increased the viscosity of the emulsions but these emulsions appeared to be less stable than the emulsions obtained with the other two surfactants. However, there was no complete breakdown of these emulsions but the oil globules increased in size due to coalescence and were visible even to the naked eye within a few days.

4.4 Conclusion

Although the liquid emulsions contained no mesophases various kinds were observed in all of the ternary systems. Friberg and co-workers have made extensive studies on the relationship between the emulsion stability and the formation of mesomorphous phases (Friberg et al., 1969; Friberg et al., 1970 a and b; Friberg et al., 1976). These workers have proposed a mechanism for emulsion stabilization. When emulsion droplets approach each other, there will be a temporary rise of emulsifier concentration in the region between the drops. If the ratio of the emulsifier to oil is increased and the water content reduced, the three components will form ordered structures, such as liquid

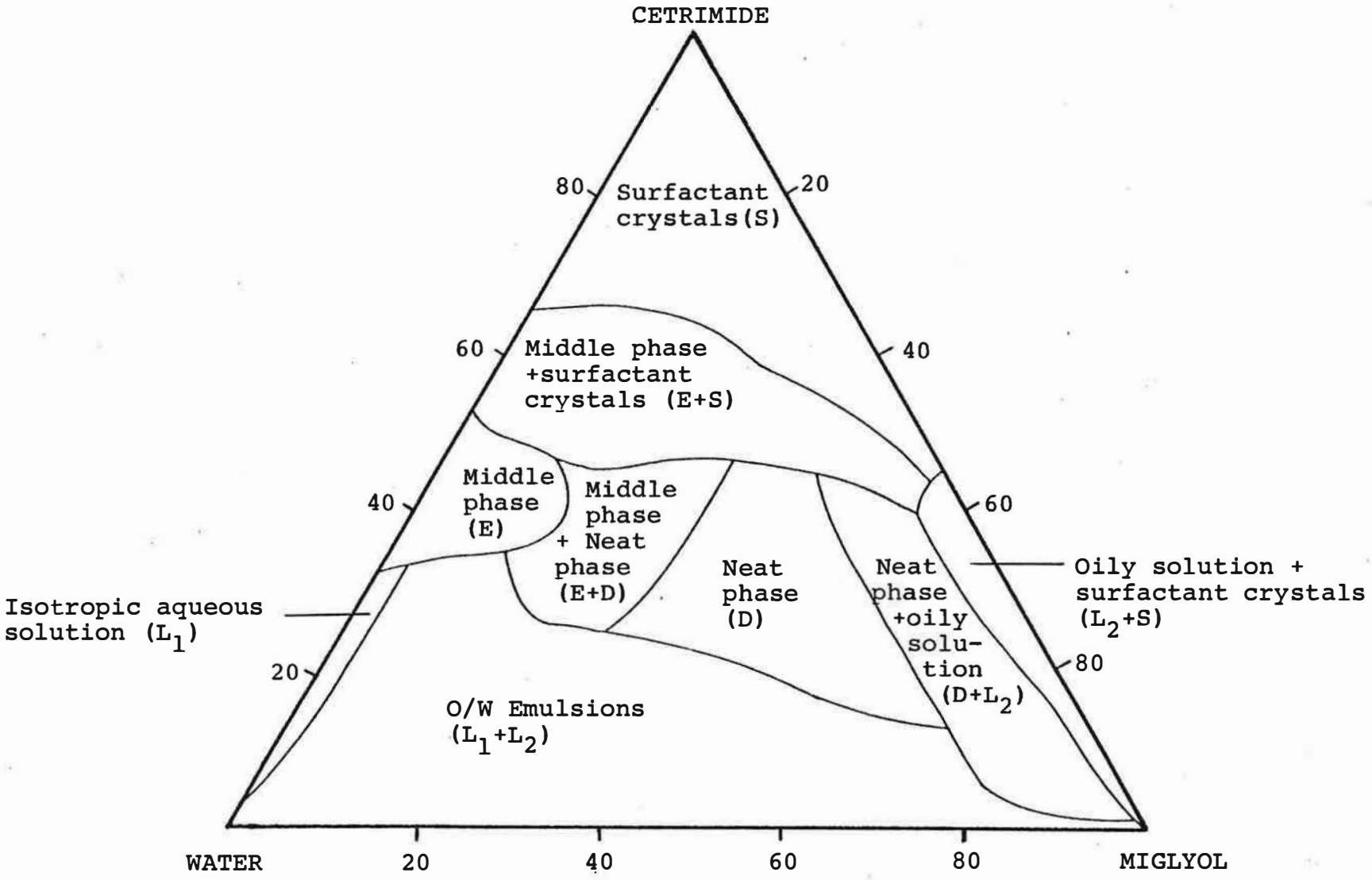


Figure 4.3. Ternary phase diagram of water/Miglyol/cetrimide at 25°C.

crystals, in the thin region and this will give stability against coalescence (Friberg et al., 1970a).

The tendency of the three components to form ordered structures has been discussed in the preceding section, where it was noted that emulsions formed in all of the ternary systems were stable. Such results were in accord with the findings of Friberg and co-workers (Friberg et al., 1969; Friberg et al., 1970 a and b; Friberg et al., 1976). Although ternary phase diagrams gave useful information about the stability and the consistency of the emulsions, no liquid emulsion with low viscosity was observed which also contained mesophases. The emulsions containing low surfactant concentrations were considered to be suitable for the drug release experiments and a 1% surfactant concentration was used in order to study the effect of the surfactant type on drug release.

CHAPTER 5

EFFECT OF FORMULATION VARIABLES ON DRUG RELEASE FROM O/W EMULSIONS

5.1 Introduction

From the preliminary drug release experiments, it was concluded that the elucidation of the mechanism of release from emulsions was a complex problem. The objective of this section of the work was to study some of the factors affecting this process. Therefore, in vitro release from various o/w emulsions was investigated as a function of the surfactant type and concentration, phase volume ratio and the nature of the drug.

5.2 Experimental

First of all, the release of the model drug, salicylic acid, from aqueous solution to an aqueous sink was used as the control for further evaluation of the suitability of the in vitro drug release method given in Chapter 2. The effect of the drug concentration, stirring rate of the donor solution and volume of the receptor solution was studied.

Nine emulsions were then prepared by varying the phase volume ratio and the total surfactant concentration. They were made according to the method described in Chapter 2 and the salicylic acid concentration was always held constant at 0.1 g/100 ml. The surfactant chosen was cetomacrogol-1000, because it produced stable emulsions and was compatible with the drug.

Apparent partition coefficients corresponding to the emulsions prepared and the solubilities of the drug in the aqueous micellar solutions were determined by the methods described in Chapter 2 and the results were used to estimate the extent of the distribution of salicylic acid in the oil, aqueous and micellar phases of the emulsions.

Drug release experiments were repeated 1 week, 6 weeks, 3 months and 6 months after the preparation of the emulsions in order to discover the effect of ageing on the drug release. The stability of these emulsions was also followed during this time and these results are reported in Chapter 6.

The receptor solutions used were distilled water and McIlvane buffer solutions at pH values of 2.2, 3.0, 5.0 and 7.0. Although there was no significant effect of the ionic strength on the release, the ionic strength of the buffer solutions was adjusted to 0.5 with potassium chloride to standardise the experimental method.

A new batch of the Visking tubing was used for these studies. Since the structure of the cellulose acetate membrane, notably the pore size, can differ slightly from batch to batch, the experiments were repeated for the control solutions to test the properties of the membrane, whenever a new batch had to be used.

In order to demonstrate the effect of the surfactant type on drug release, emulsions which were stabilized with sodium lauryl sulphate, cetrimide or Tween 20-Span 80 mixtures at varying HLB values were also studied. The phase volume ratio of the emulsions, salicylic acid concentrations and the surfactant concentrations were held constant at 50/50,

0.1% w/v and 1% w/v respectively and the receptor solution was always distilled water.

Using the same model emulsion which was prepared with 1% w/v cetomacrogol, the effect of the nature of the drug on release was also investigated. Benzoic acid, 3-hydroxy benzoic acid, aspirin, paracetamol and phenacetin were the drugs studied.

Miglyol 829 which is a more viscous oil than Miglyol 812, and Miglyol-812 gelled with some gelling agents, were used to prepare emulsions in order to evaluate the effect of the viscosity of the oil phase on drug release from emulsions. Miglyol gels alone were also tested for drug release. For this portion of the study, salicylic acid was again the model drug and cetomacrogol was used to stabilize the emulsions. Miglyol-Gel, Bentone 34, Bentone 38, Aerosil 200 and Aerosil 300 were the gelling agents used at varying concentrations to produce oily gels having different viscosities.

5.3 Results and Discussion

5.3.1 The effect of the stirring rate of the donor solution on salicylic acid release

The effect of the stirring rate on the drug release from the standard aqueous salicylic acid solution of 0.1% w/v was studied at 25, 50 and 75 rpm.

Results are shown in Figure 5.1 and Table 5.1. The slopes of the lines for the stirring rates of 50 and 75 rpm were not significantly different and were within the limits of ± 3% of the mean value. However, at the slowest stirring rate, 25 rpm, the release was the slowest suggesting the existence of a diffusion layer building up on the donor side of the membrane.

Table 5.1. Effect of the stirring rate of the donor cell on salicylic acid release from the standard aqueous solution.

Donor solution conc. % w/v	Stirring rate of donor solution	Slope $cm^3\ min^{-1}$	Correlation coefficient	Degrees of freedom
0.1	25 rpm	0.0486	0.9985	74
	50 rpm	0.0560	0.9931	134
	75 rpm	0.0588	0.9950	54

Table 5.2. Effect of the salicylic acid concentration on release from the aqueous solutions.

Donor solution conc.% w/v	Receptor solution	Slope $cm^3\ min^{-1}$	Correlation coefficient	Degrees of freedom
0.20	D. water	0.0548	0.9869	23
0.10	D. water	0.0560	0.9931	134
0.05	D. water	0.0560	0.9938	67

Table 5.3. Effect of the receptor volume on salicylic acid release from the standard aqueous solution.

Donor solution	Receptor volume	Slope $cm^3\ min^{-1}$	Correlation coefficient	Degrees of freedom
0.1% w/v	50	0.0560	0.9931	134
	100	0.0559	0.9996	90

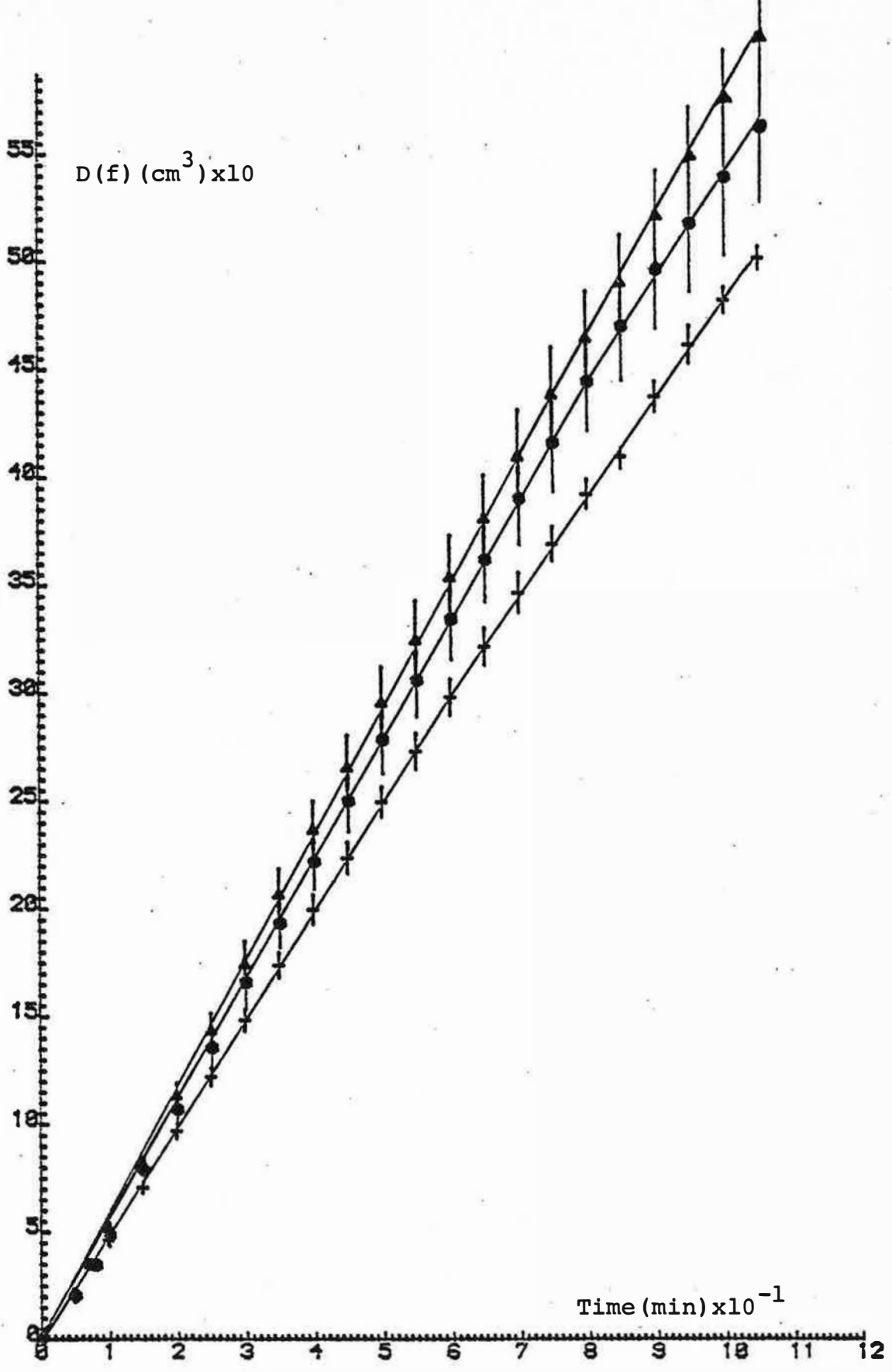


Figure 5.1. Effect of stirring rate of donor cell on salicylic acid release from aqueous solution. (+) 25 rpm, (●) 50 rpm, (▲) 75 rpm.

Although there was no significant difference between the slopes at the stirring rates of 50 and 75 rpm, the optimum rotation speed, 50 rpm, was used for all subsequent studies to ensure efficient mixing without turbulence.

5.3.2 The effect of the drug concentration on release from the aqueous solutions

In order to evaluate the suitability of the in vitro drug release method, the release of salicylic acid from 0.05, 0.1 and 0.2% w/v solutions was investigated. The results being shown in Figure 5.2 with the corresponding slopes being summarized in Table 5.2. Since there was no significant difference between the slopes, it was concluded that the release rate of salicylic acid through cellulose acetate membrane does not depend on the initial concentration in the drug compartment.

5.3.3 Effect of the receptor volume on salicylic acid release

In order to demonstrate the effect of the sink volume, similar experiments were carried out with 50 ml and 100 ml of the receptor solutions. The results, presented in Figure 5.3 and Table 5.3, show that a 50 ml volume was sufficient to act as a sink and this receptor volume was used for subsequent experiments. These results also indicate that the slight levelling off on most of the release curves cannot be attributed to a back diffusion of the drug during the experiments (Figure 5.3).

5.3.4 Drug release from cetomacrogol-1000 emulsions

In an effort to understand the mechanism of the release

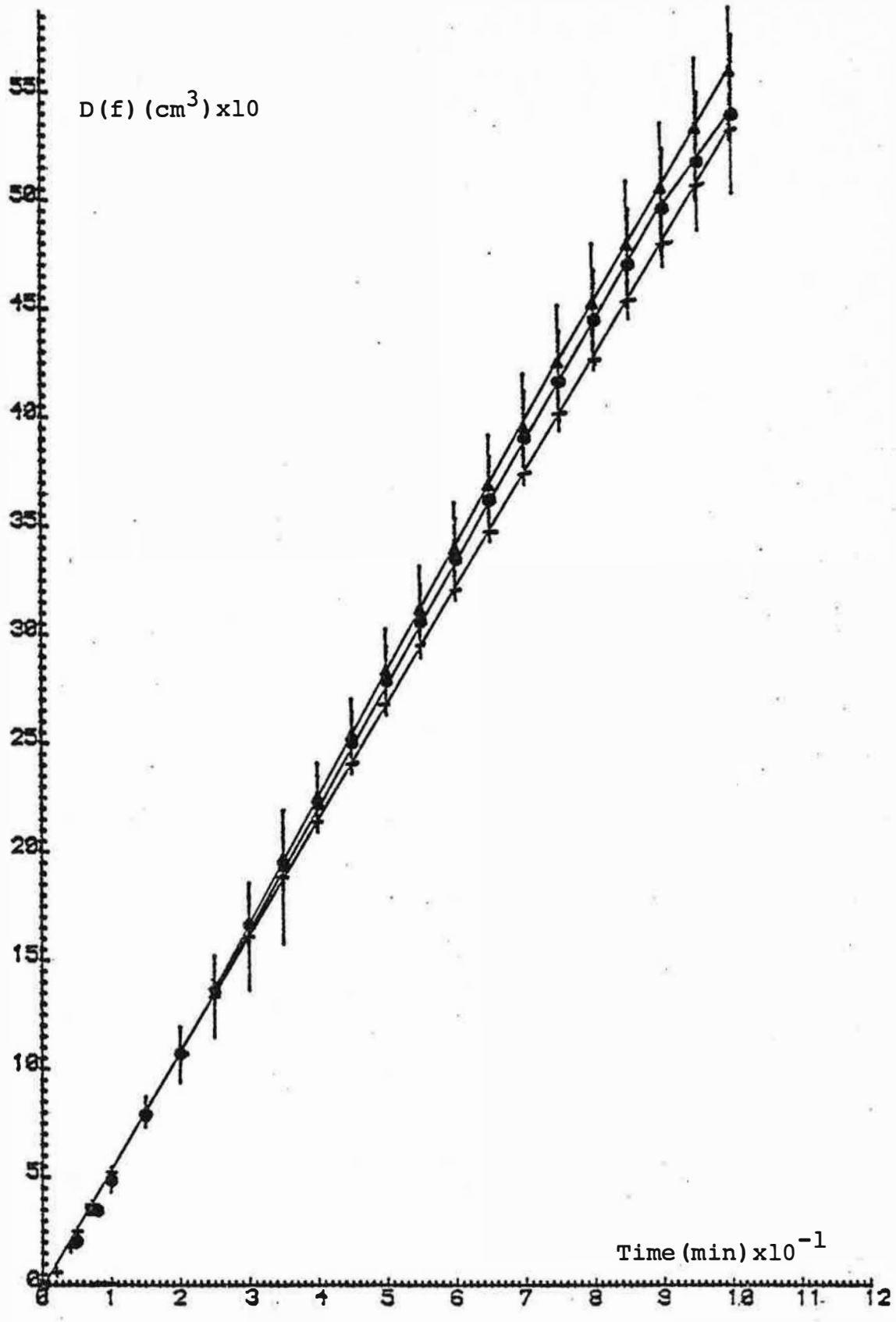


Figure 5.2. Effect of salicylic acid concentration of donor solution on release. (▲) 0.05% w/v, (●) 0.10% w/v, (+) 0.20% w/v.

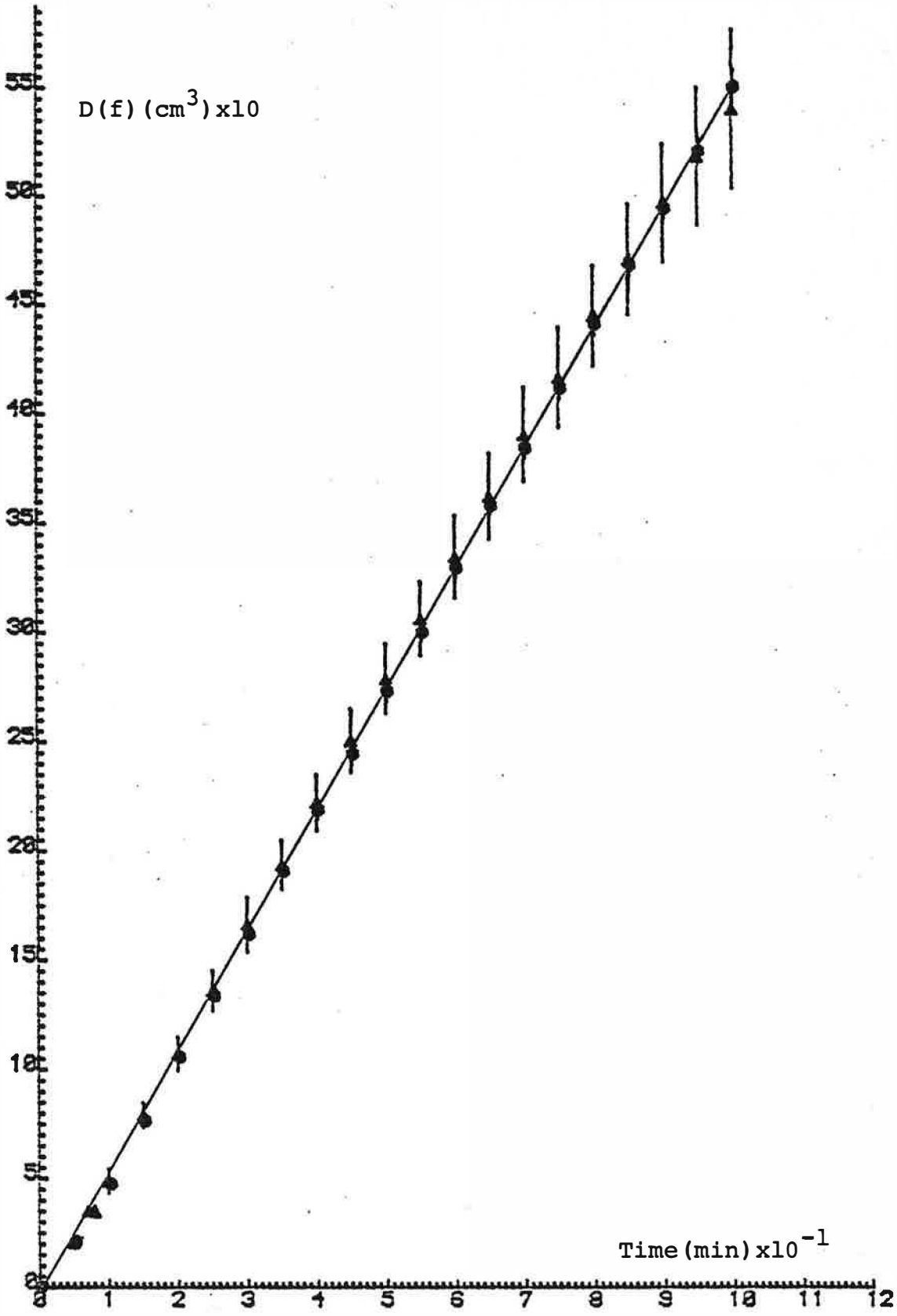


Figure 5.3. Effect of receptor volume on salicylic acid release. (▲) 50 ml, (●) 100 ml.

of salicylic acid from o/w emulsions, nine emulsions were prepared with different concentrations of cetomacrogol-1000 or with different oil/water phase volume ratios (Table 5.4). It was considered that release from these emulsions might demonstrate not only the effect of the surfactant concentration and the phase volume ratio, but also the effect of the micellar phase and any possible difference in the interfacial film on drug release from an o/w emulsion.

5.3.4.1 Solubilization of salicylic acid in cetomacrogol micelles

Solubility experiments were carried out in order to establish the amount of drug solubilized in the micellar phase. These results were used to calculate the ratio of the total/free drug, given by equation (3.12),

$$R = \frac{C_w}{C_{free}} \qquad (3.12)$$

where C_w is the total salicylic acid concentration and C_{free} is the non-micellar salicylic acid concentration respectively. Assuming that distribution of surfactant in the oil phase of the emulsion and at the interface did not significantly reduce the amount of surfactant initially in the aqueous phase of the emulsion, the total and the free aqueous salicylic acid concentrations were determined and the corresponding R ratios were calculated (Table 5.5). When the total salicylic acid concentrations and the R ratios were plotted against the surfactant concentration (Figure 5.4 and Figure 5.5 respectively), there was a good linear relationship in each case. There have been a number of publications showing similar relationship

Table 5.4. The composition of the cetomacrogol emulsions.

Emulsion No.	Water % v/v	Miglyol % v/v	Cetomacrogol-1000 % w/v
II-1	80	20	0.5
II-2	60	40	0.5
II-3	40	60	0.5
II-4	80	80	1.0
II-5	60	40	1.0
II-6	40	60	1.0
II-7	80	80	3.0
II-8	60	40	3.0
II-9	40	60	3.0

Table 5.5. Solubilization of salicylic acid by cetomacrogol-1000 at 37±1°C.

Concentration of Cetomacrogol-1000 % w/v	Solubility of salicylic acid %w/v	R; $\frac{C_w}{C_{free}}$
0	0.338 ±0.002	1
0.004	0.33 ±0.000	0.9986
0.625	0.475 ±0.008	1.4065
0.833	0.548 ±0.003	1.6229
1.000	0.568 ±0.004	1.6825
1.250	0.638 ±0.004	1.8872
1.667	0.746 ±0.000	2.2082
2.000	0.804 ±0.001	2.3806
2.500	0.949 ±0.067	2.8077
3.750	1.239 ±0.003	3.6667
5.000	1.546 ±0.018	4.5733
7.500	2.168 ±0.039	6.4148

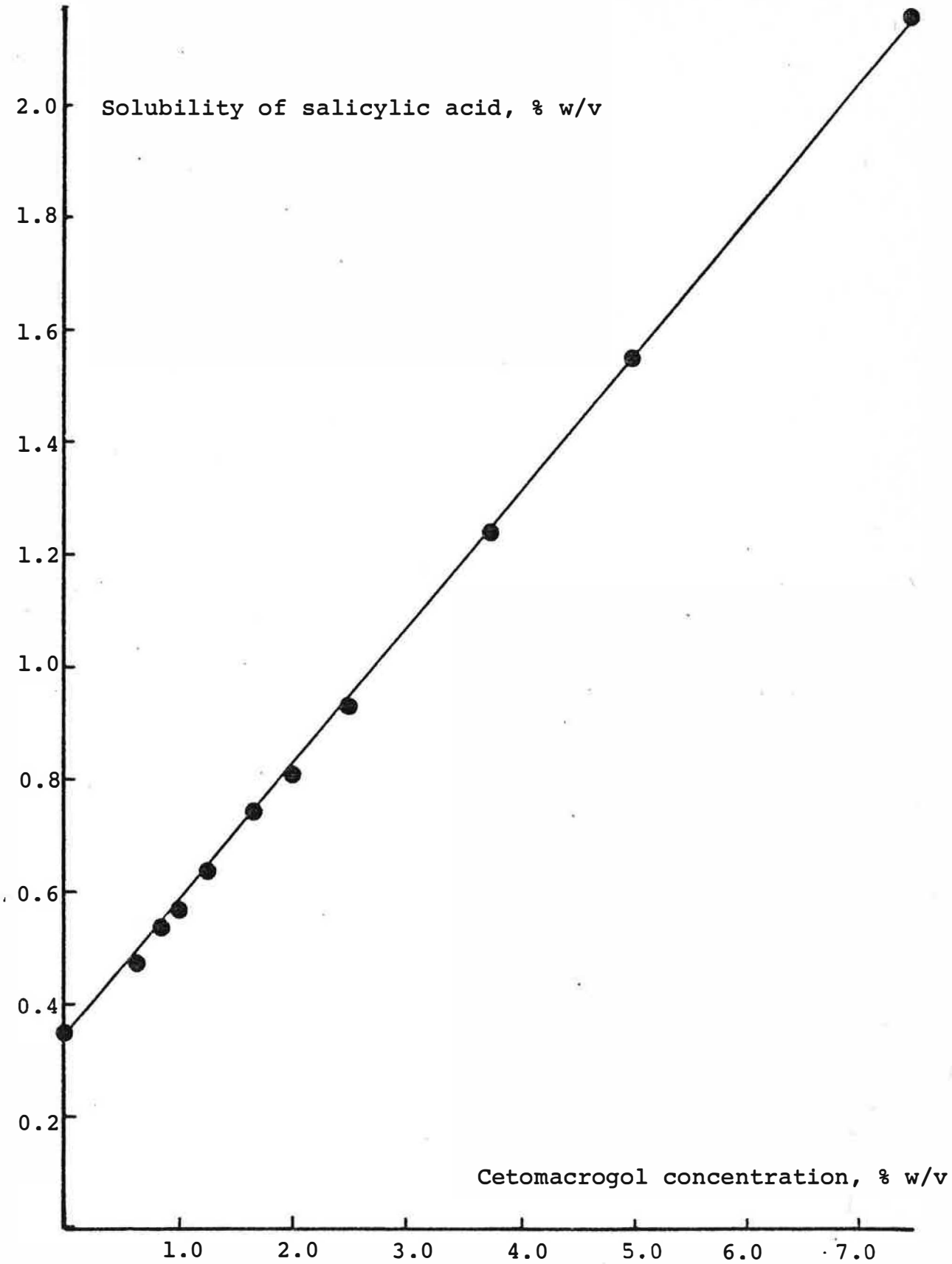


Figure 5.4. Salicylic acid solubilization at 37°C as a function of cetomacrogol concentration.

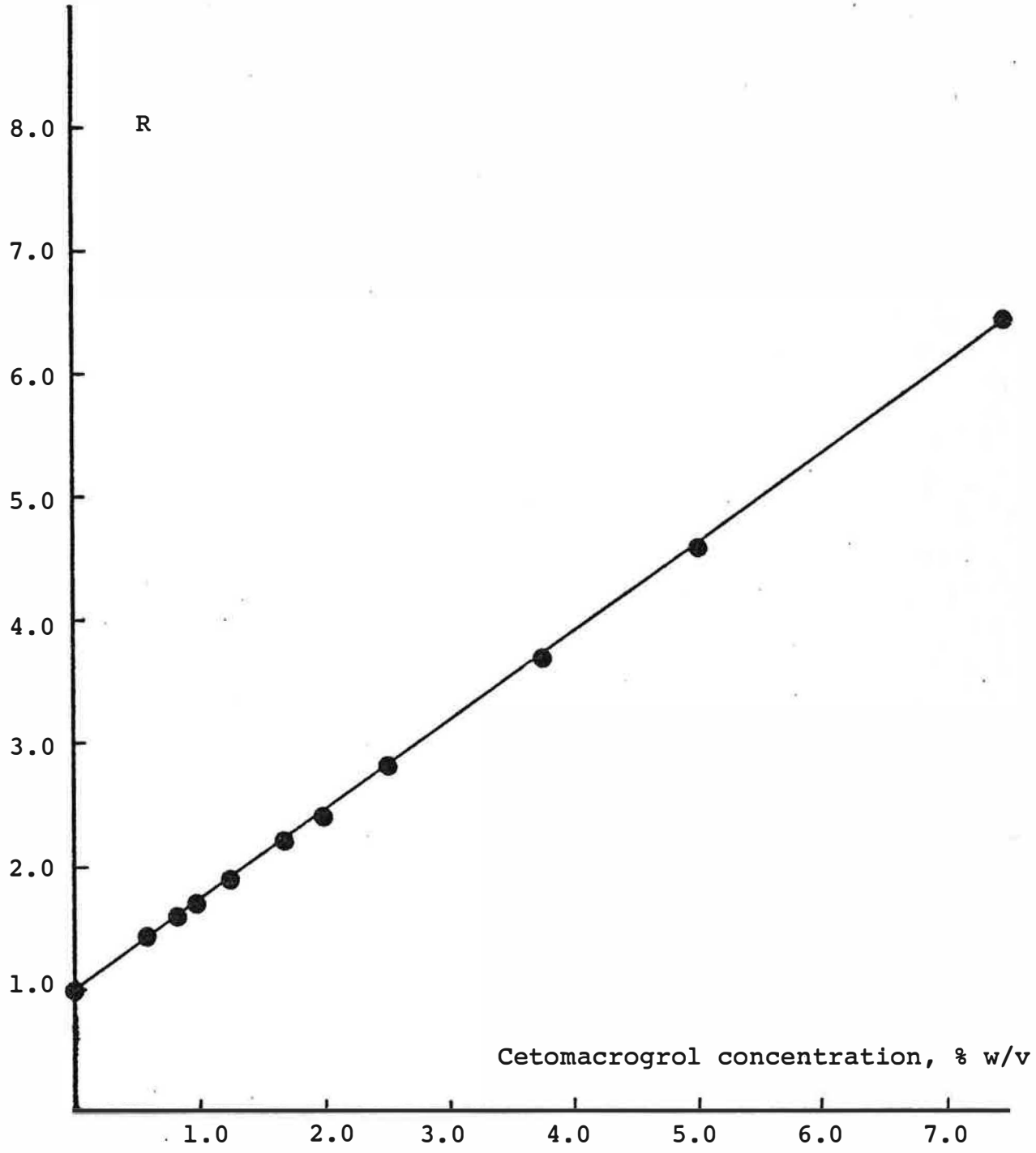


Figure 5.5. Relationship between ratio, R, of total to free salicylic acid and cetomacrogol concentration.

between the surfactant concentration and the concentration of drug solubilized or the R ratios (Patel and Kostenbauder, 1958; Matsumoto, Matsumaro and Iguchi, 1966a; Short, Abbs and Rhodes, 1970; Juni, Nakano and Arita, 1977). The solubilization of a drug in the micellar phase of an emulsion could influence the release properties considerably by reducing the amount of drug partitioning into the oil and aqueous phases. Also, any contribution of the micellar phase of the emulsion to the release could further change the release properties of the system and this could be used as an important tool in biopharmaceutical design (Anderson et al., 1981; Schumacher, 1971b).

5.3.4.2 Effect of cetomacrogol concentration on salicylic acid release from the micellar solutions

The release of salicylic acid from the micellar solutions was studied in order to demonstrate the effect of micellar entrapment of the drug on its release. The concentration of salicylic acid was held constant at 0.1% w/v and the amount of cetomacrogol was varied. Results of these release experiments are presented in Figure 5.6 and the slopes of the lines are summarized in Table 5.6, where it can be clearly seen that there was a significant decrease in drug release with increasing amount of cetomacrogol above the CMC. However, no effect was observed when the concentration of cetomacrogol was less than the CMC, which is 0.006-0.007% in water (Florence and Rogers, 1971), suggesting that the interaction between the surfactant and salicylic acid was due only to micellar solubilization. When the slopes were

Table 5.6. Effect of cetomacrogol-1000 concentration on salicylic acid release from the micellar solutions.

Cetomacrogol-1000 concentration % w/v	Slope $cm^3\ min^{-1}$	Correlation coefficient	Degrees of freedom
0.00	0.0560	0.9931	134
0.004	0.0561	0.9926	74
0.5	0.0419	0.9616	74
1.0	0.0319	0.9557	74
2.0	0.0218	0.9973	54
3.0	0.0170	0.9929	44
4.0	0.0147	0.9977	67
5.0	0.0132	0.9976	64
6.0	0.0103	0.9990	67
7.0	0.0104	0.9998	66

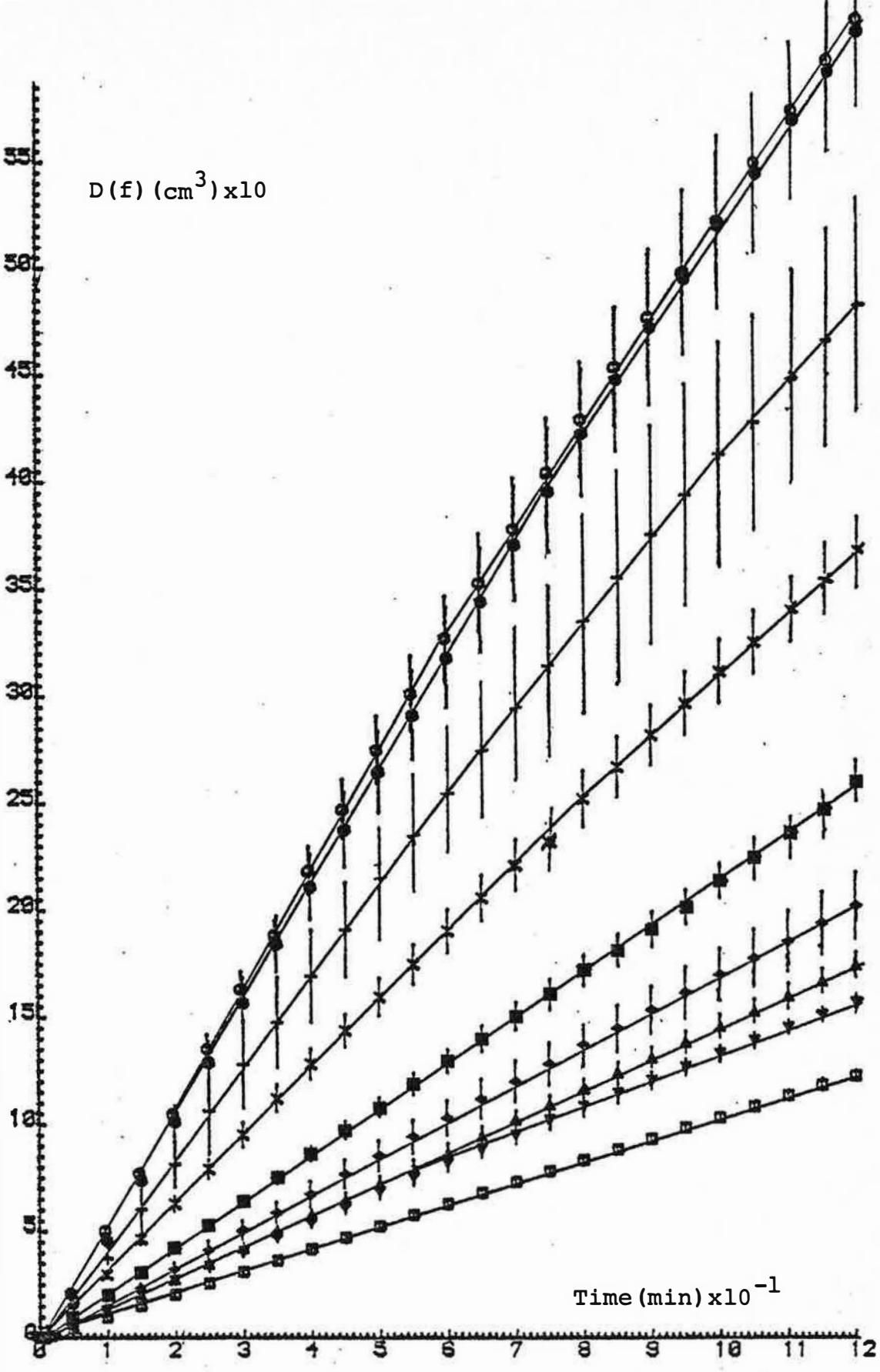


Figure 5.6. Effect of cetomacrogol concentration (% w/v) on salicylic acid release from micellar solutions. (●) 0.0, (○) 0.004, (+) 0.5, (×) 1.0, (■) 2.0, (◆) 3.0, (▲) 4.0, (▼) 5.0, (□) 6.0 α 7.0.

plotted against the concentration of the surfactant and the R ratio as shown in Figure 5.7, the relationship was not linear. A similar non-linear inverse relationship between the drug release and the surfactant concentration or the R ratio has been reported by Matsumoto (1966). These researchers first suggested that the drug molecules in the micellar phase also dialyse into the outer fluid through any route, but further studies showed there to be no direct dialysis of a dye, yellow AB, from the micellar phase. They, therefore, concluded that direct dialysis from micelles into the outer fluid was negligible and that the drug molecules in the micellar phase rapidly transferred to the aqueous phase and then participated in the dialysis (Matsumoto et al., 1966 a and b). Contrary to this, Short et al. (1970) reported a linear relationship between the testosterone diffusion coefficient and the surfactant concentration present, but extrapolation to zero surfactant concentration yielded a value substantially different from the diffusion coefficient of testosterone determined in distilled water. Since the solutions used in this investigation were stirred during the membrane diffusion measurements and there was no permanent interference with the integrity of the membrane, the depressant effect of the surfactant on the steroid transport was attributed to either a generalized inhibition of adsorption at the membrane-solution interface or competition between the monomeric surfactant and steroid for adsorption sites upon the membrane (Short et al., 1970). Instantaneous partitioning of drug back into the bulk solution, when its concentration is decreased due to permeation through a membrane, appears to

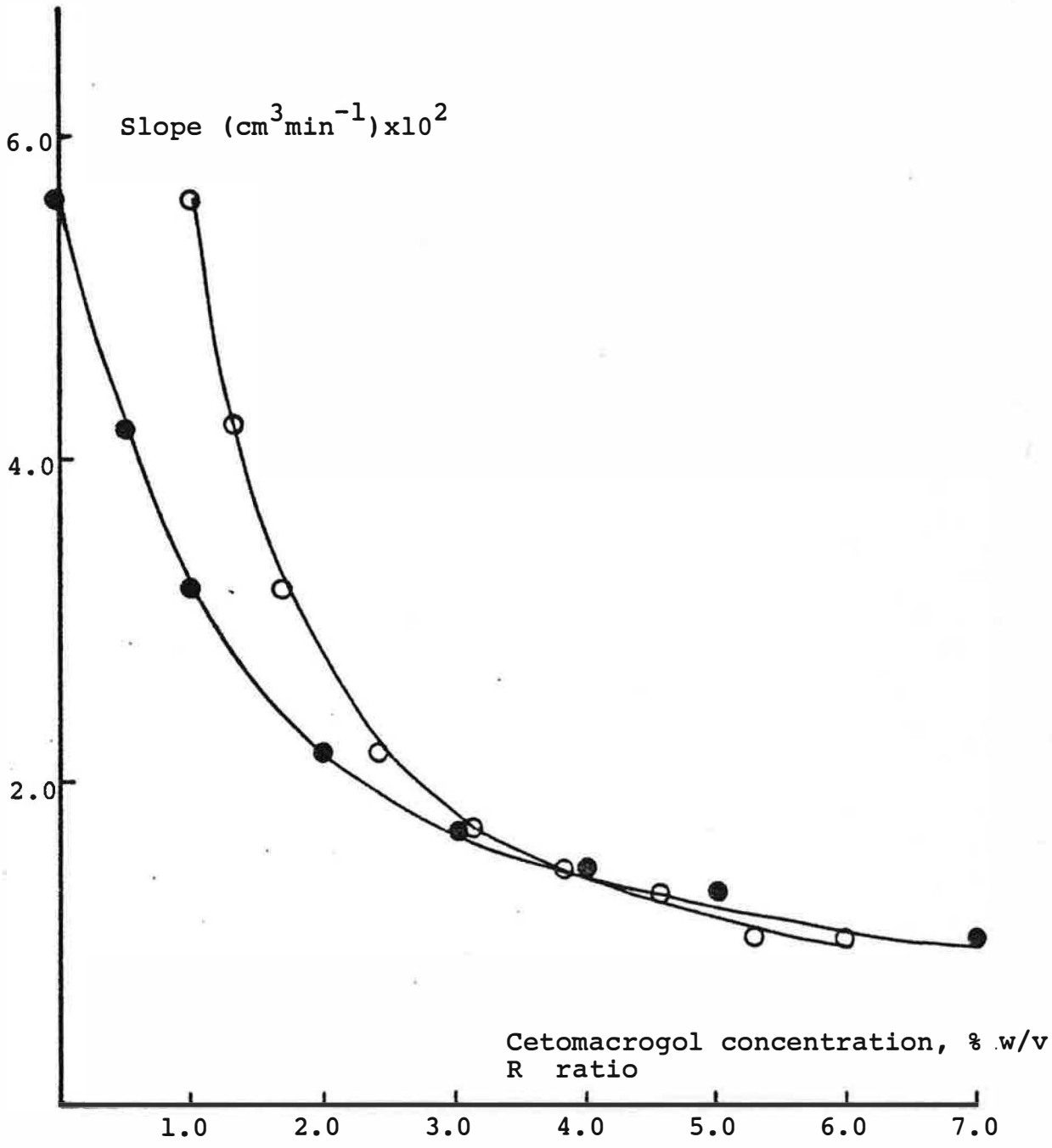


Figure 5.7. Effect of cetomacrogol concentration (●) and R ratio (○) on salicylic acid release from micellar solutions.

be the usually accepted explanation for this process in many of the other publications (Creovisier, Buri, Boucherat, 1974; Juni et al., 1977; Juni et al., 1978). Recently, however, Collett and Dickinson (1980) have reviewed the previous reports and studied the mechanism of drug release from micellar solutions. These workers concluded that the micellar solution acted as two kinetically distinguishable compartments and the micellar solubilizate was mainly transferred to the aqueous environment as a result of complete dissolution of a micelle and only to a lesser extent as a result of diffusion from a micelle. As the surfactant concentration increased, the rate constants for transfer from the non-micellar region did not show a marked change (Collett et al., 1980). This was in good agreement with the present results that when the slopes were plotted against the free drug concentrations (Table 5.7), there was a linear relationship as shown in Figure 5.8. Thus, under the experimental conditions, the effective concentration which governed the release from the micellar solution was the non-micellar salicylic acid concentration only.

5.3.4.3 Determination of the apparent partition coefficients

Partition study was undertaken in order to estimate the extent of salicylic acid distribution between the oil and aqueous phases of the emulsions. The micellar and non-micellar aqueous concentrations were also calculated by using the corresponding R values determined from the solubility experiments. The apparent partition coefficients and the other calculated variables are summarized in Table 5.8. The

Table 5.7. Effect of free drug concentration on drug release from micellar solutions.

Cetomacrogol-1000 concentration % w/v	Free drug concentration % w/v	Slope $cm^3\ min^{-1}$
0.00	0.1	0.0560
0.004	0.0999	0.0561
0.5	0.0744	0.0419
1.0	0.0587	0.0319
2.0	0.0412	0.0218
3.0	0.0318	0.0170
4.0	0.0259	0.0147
5.0	0.0218	0.0132
6.0	0.0188	0.0103
7.0	0.0166	0.0104

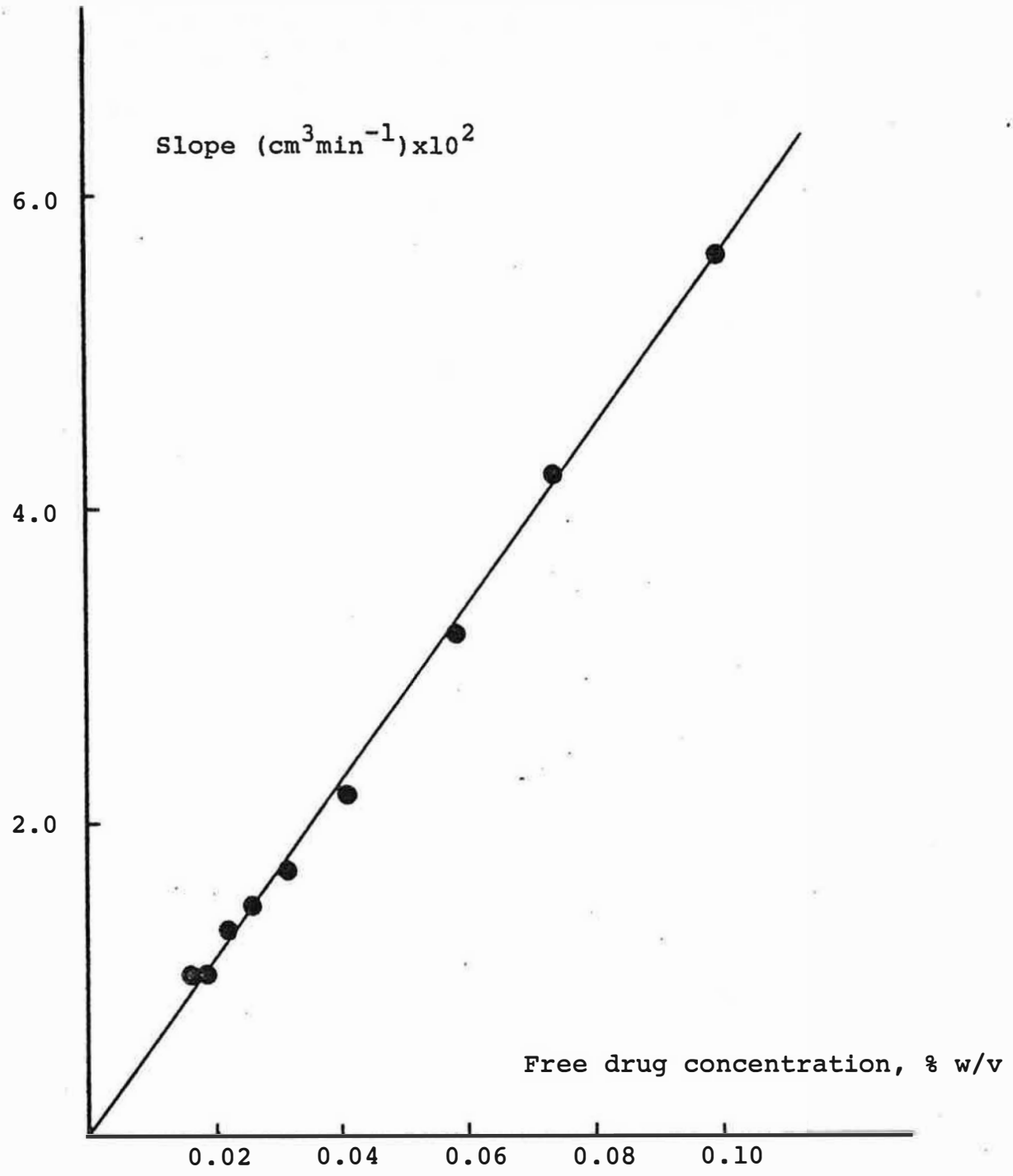


Figure 5.8. Relationship between the free salicylic acid concentration and the release from micellar solution.

Table 5.8. Partition coefficients and the extent of the drug distribution in the oil and aqueous phases of the emulsions.

Emulsion	$\phi = \frac{\text{Oil(v)}}{\text{Water(v)}}$	Cetomacrogol % w/v	C_w % w/v	C_{free} % w/v	M_w (g. in aqueous phase)	M_{free}	C_o % w/v	M_o (g.in oil phase)	$K_{app.}$	K_{free}
II-1	20/80	0.5	0.0312	0.0222	0.0250	0.0178	0.3775	0.0751	12.01	16.89
II-2	40/60	0.5	0.0229	0.0141	0.0137	0.0085	0.2159	0.0864	9.44	15.32
II-3	60/40	0.5	0.0209	0.0111	0.0084	0.0044	0.1526	0.0916	7.29	13.77
II-4	20/80	1.0	0.0385	0.0204	0.0308	0.0163	0.3462	0.0692	8.99	16.96
II-5	40/60	1.0	0.0300	0.0136	0.0180	0.0082	0.2049	0.0819	6.83	15.07
II-6	60/40	1.0	0.0297	0.0106	0.0119	0.0042	0.1469	0.0881	4.94	13.87
II-7	20/80	3.0	0.0627	0.0171	0.0501	0.0137	0.2494	0.0499	3.98	14.59
II-8	40/60	3.0	0.0543	0.0119	0.0326	0.0071	0.1684	0.0674	3.10	14.18
II-9	60/40	3.0	0.0599	0.0093	0.0240	0.0037	0.1267	0.0760	2.11	13.56

apparent partition coefficients changed significantly with increasing surfactant concentrations, even when the phase volume ratio was kept constant, due to the increasing entrapment of the drug in the micelles. When the partition coefficients of non-micellar drug for all systems were calculated as given in Table 5.8, a slight variation was observed between the partition coefficients corresponding to the emulsions having the same phase volume ratio. The reason for this lay in the differences between the experimental conditions used to determine the partition coefficients where the ionization was not controlled, and the R ratios where the pH of the saturated solutions was 2.4 and the ionization of the drug was not significant. However, although the micellar and non-micellar aqueous drug concentrations and calculated K values were only approximate, the apparent partition coefficients still represented the actual distribution of the drug between the oil and the aqueous phase (micellar plus non-micellar) of each emulsion.

The prognostic significance of the partitioning properties of a drug in formulation studies has been discussed in a number of papers (Bean et al., 1970; Schumacher, 1971 a and b; Kakemi et al., 1972a; Anderson et al., 1981). Since the amount of salicylic acid present in the oil and aqueous phases of the emulsions were always different, the release characteristics of these nine emulsions prepared are expected to be different and this is discussed in the following section.

5.3.4.4 Salicylic acid release from emulsions

5.3.4.4.1 Salicylic acid release from emulsions to distilled water

The release characteristics of the emulsions having identical phase volume ratios were the same, even though the drug concentrations in the oil and aqueous phases, both micellar and non-micellar, were different for each emulsion (Table 5.9). As previously discussed, salicylic acid release from micellar solution to distilled water depends on its non-micellar concentration (Figure 5.8). When the calculated aqueous free salicylic acid concentrations were plotted against the slopes of the release curves (Figure 5.9) the correlation coefficient of the common line was 0.9643, however emulsions containing higher concentrations of cetomacrogol showed slightly faster release of salicylic acid. This could suggest either that there was a contribution of the micellar phase to the release or the calculated free drug concentrations were not correct due to the different experimental conditions used for these calculations as mentioned before. Kakemi et al. (1972a) suggested that the amount of a drug in aqueous phase is a critical factor for the absorption from o/w emulsions rather than the total concentration. In their studies, the concentration of the surfactant was kept low at 0.1% and the micelles were found only in the oil phase, therefore the amount of the drug in the aqueous phase was only the non-micellar component. When the slopes given in Table 5.9 were plotted against M_{free} (Figure 5.10), similar correlation as in Figure 5.9 was observed, indicating that the release from the emulsions containing higher surfactant

Table 5.9. Salicylic acid release from emulsions to distilled water 1 week after the preparation.

Emulsion No.	ϕ v/v	Slope $cm^3\ min^{-1}$	Correlation coefficient	Degrees of freedom
II-1	20/80	0.0115	0.9927	74
II-2	40/60	0.0072	0.9812	50
II-3	60/40	0.0045	0.9892	90
II-4	20/80	0.0113	0.9910	90
II-5	40/60	0.0070	0.9974	67
II-6	60/40	0.0043	0.9933	90
II-7	20/80	0.0104	0.9960	90
II-8	40/60	0.0069	0.9962	90
II-9	60/40	0.0045	0.9793	90

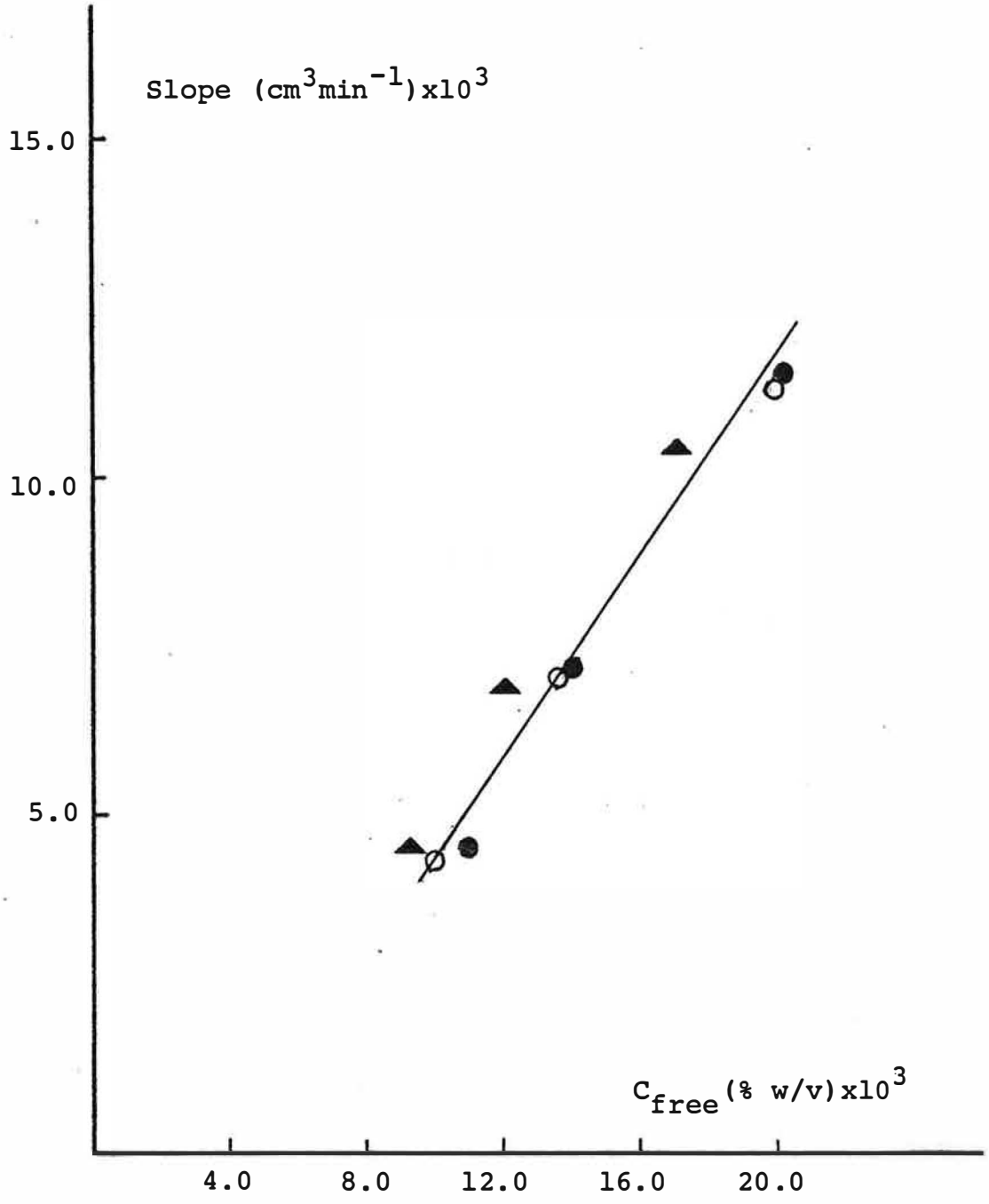


Figure 5.9. Effect of non-micellar drug concentration, C_{free}, of the aqueous phase of the emulsions on release. Cetomacrogol concentration (% w/v), (●) 0.5, (○) 1.0, (▲) 3.0.

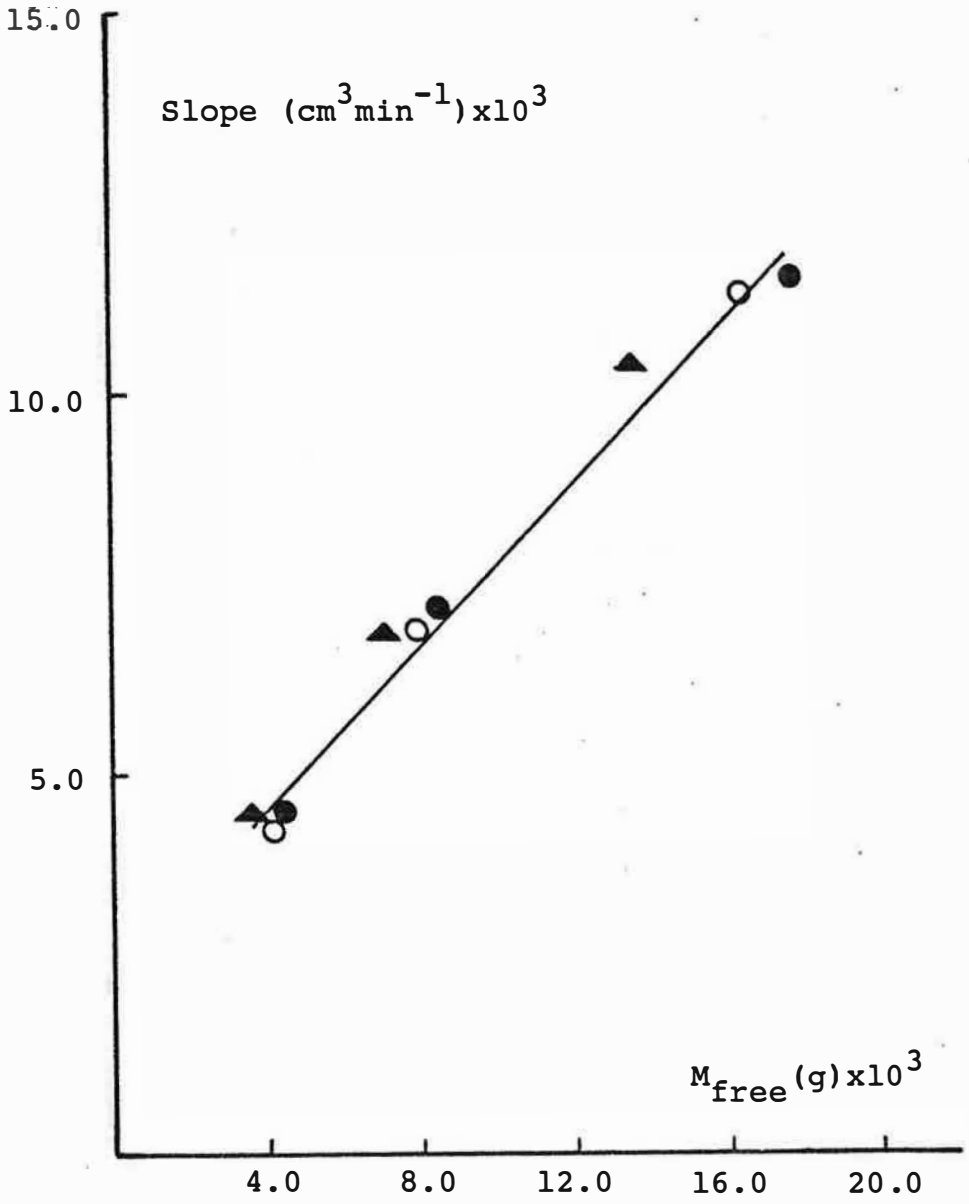


Figure 5.10. The effect of the amount of non-micellar drug, M_{free}, in the aqueous phases of the emulsions on release. Cetomacrogol concentration, % w/v; (●) 0.5, (○) 1.0, (▲) 3.0.

concentrations was slightly faster than expected. In order to investigate further whether the critical factor was the amount or the concentration of the drug in the aqueous phase, the release experiments were repeated using the isolated aqueous phases of the two emulsions (Emulsion II-7 and 9), as donor solutions. The reasons for choosing these two aqueous phases were; (a) both had high micellar concentrations, (b) they represented phase volume ratios of 20/80 and 60/40 respectively. Due to the difficulty in separating the aqueous phases of the emulsions, these donor solutions were obtained from the partition coefficient experiments corresponding to emulsions 7 and 9, and the volumes used were 80 ml and 40 ml to represent the volumes of the aqueous phases of the emulsions 7 and 9. The results are given in Figure 5.11. Slopes of these curves which are very much higher than the slopes calculated for the corresponding emulsions, 0.0104 cm^3 min^{-1} and 0.0045 cm^3 min^{-1} respectively, are shown in Table 5.10.

All of these results presented above suggested that, at least under the experimental conditions, the drug release was not controlled by the aqueous phases of the o/w emulsions and the oil phase played an important role. When the slopes of the lines were plotted against the amount of salicylic acid in the oil phases (Figure 5.12) and the apparent partition coefficients (Figure 5.13), the points did not show any overall correlation but they formed three distinct groups each representing a different oil/water volume ratio. The slopes were an inverse function of the oil/water volume ratios which can also be seen in Figure 5.14. Statistical analysis of the lines shown in Figures 5.9, 5.10, 5.12, 5.13

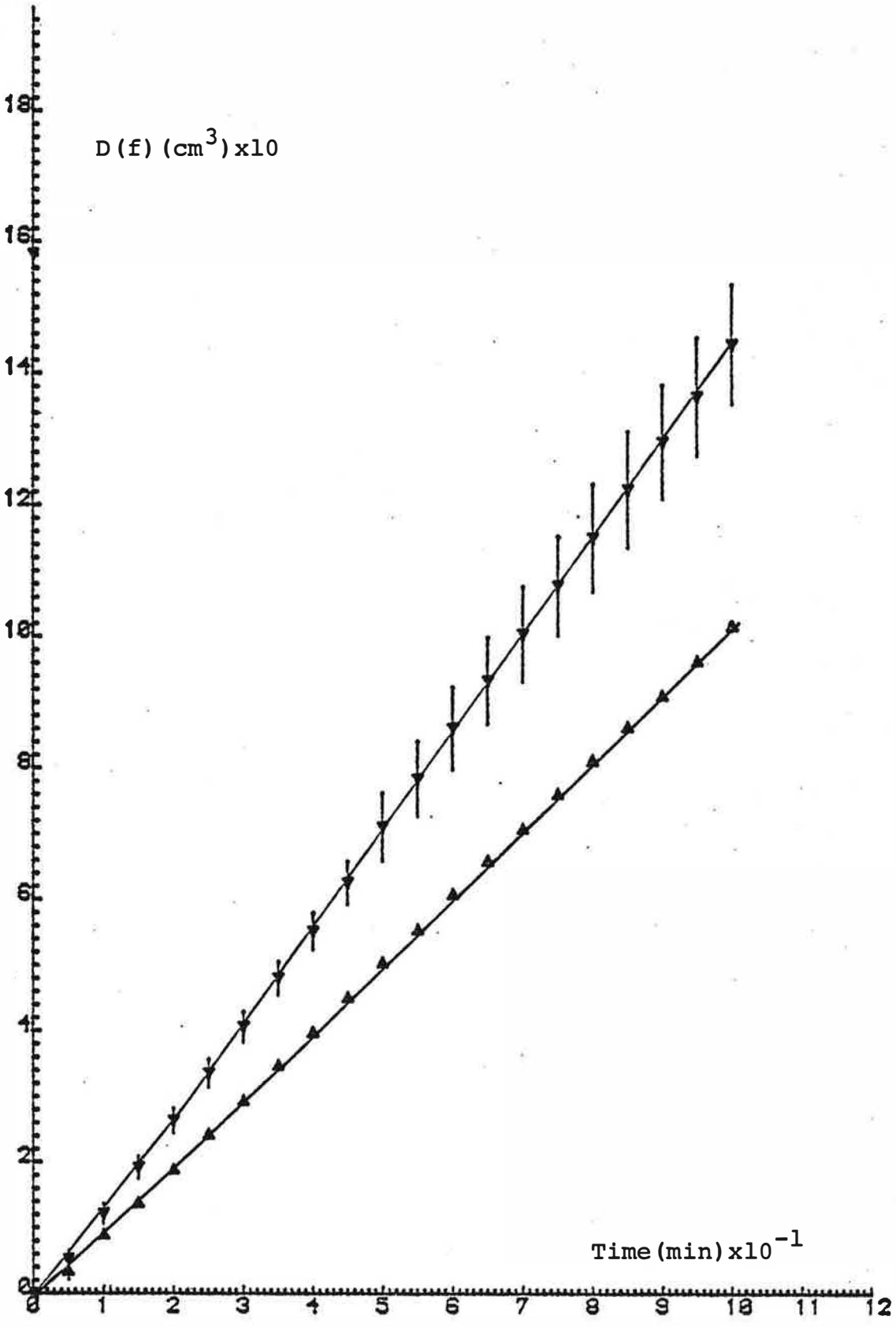


Figure 5.11. Salicylic acid release from the aqueous phases of emulsions. (▼) Emulsion II-7, (▲) Emulsion II-9.

Table 5.10. Salicylic acid release from the aqueous phases of the emulsions to distilled water.

Emulsion	Slope $cm^3\ min^{-1}$	Correlation coefficient	Degrees of freedom
II-7	0.0148	0.9943	34
II-9	0.0104	1.0	17

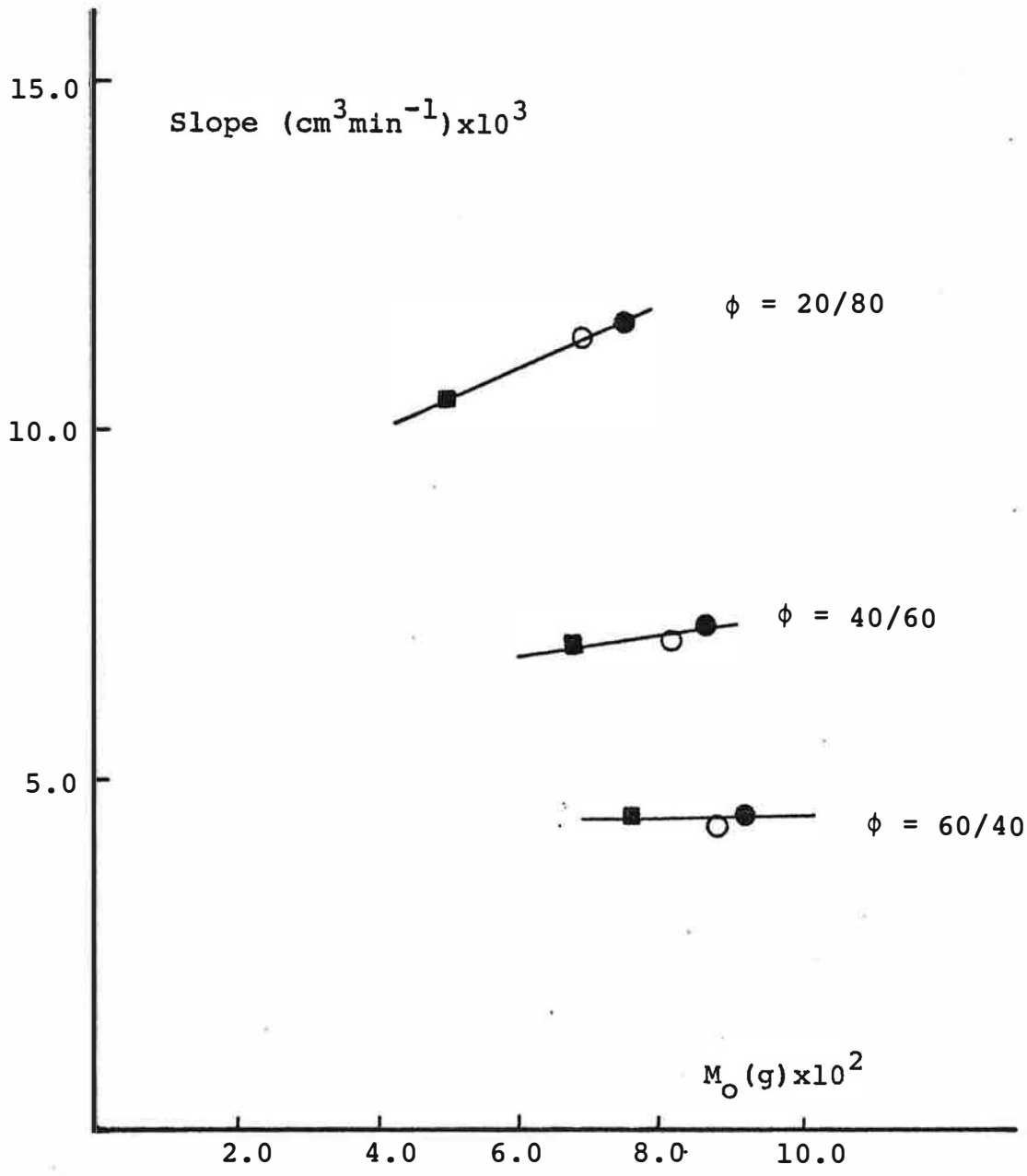


Figure 5.12. Effect of the amount of drug in the oil phases of the emulsions on release. Cetomacrogol concentration, % w/v; (●) 0.5, (○) 1.0, (■) 3.0.

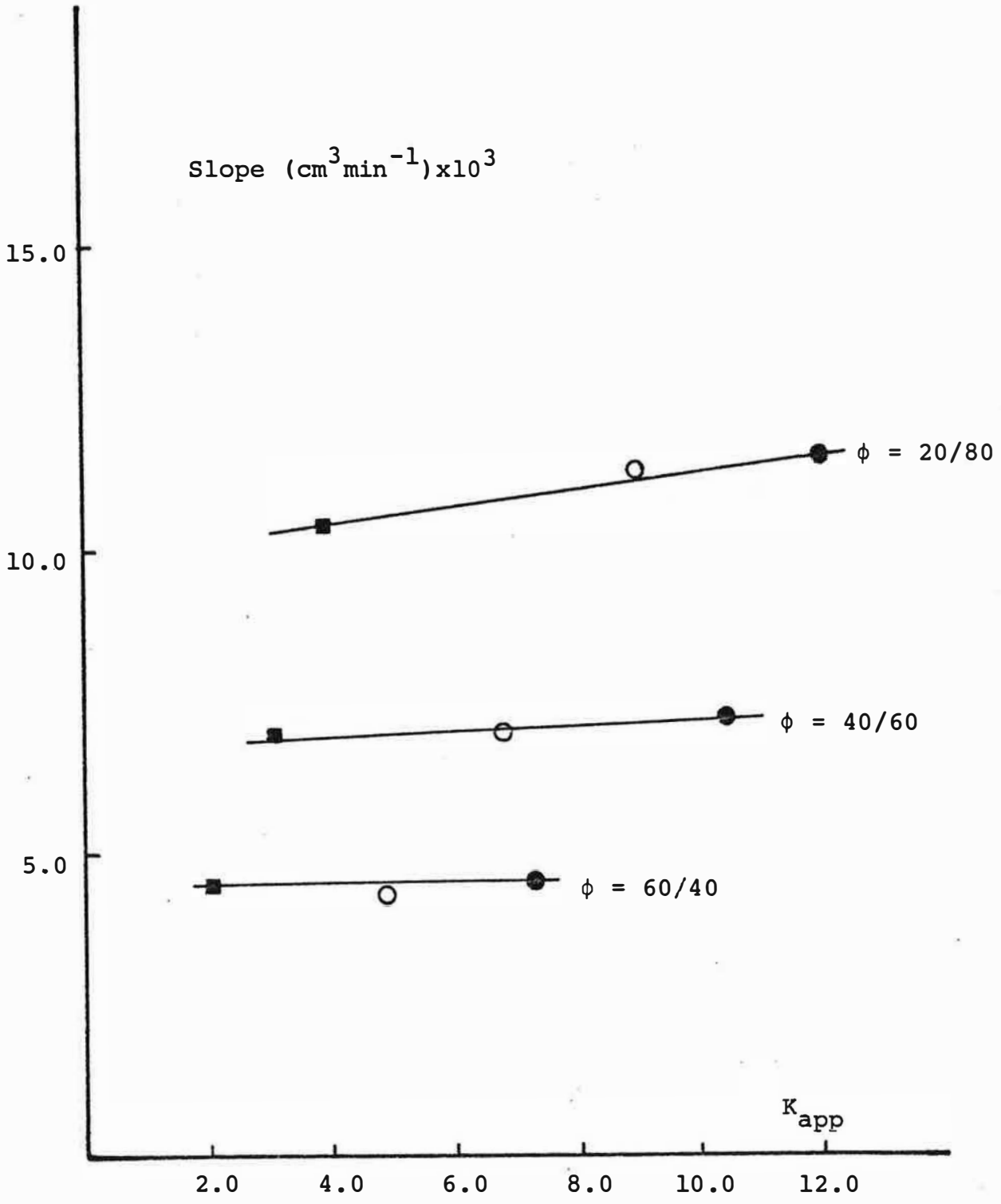


Figure 5.13. Effect of apparent partition coefficient, K_{app}, on drug release from emulsions. Cetomacrogol concentration, % w/v; (●) 0.5, (○) 1.0, (■) 3.0

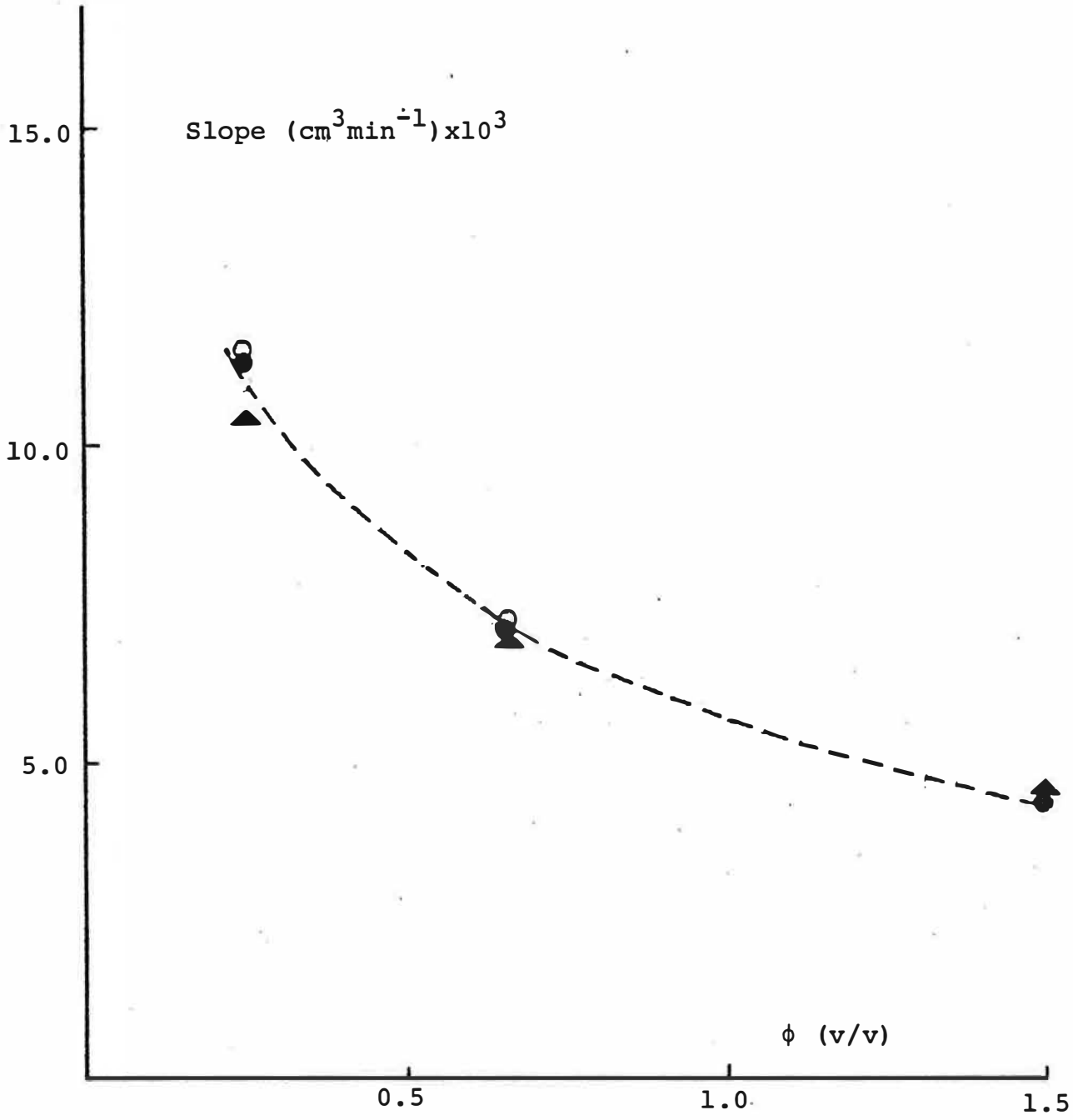


Figure 5.14. Effect of phase volume ratio, ϕ, on drug release from emulsions. Cetomacrogol concentration, % w/v; (○) 0.5, (●) 1.0, (▲) 3.0.

and 5.14 are given in Appendix III. From all of the above one may conclude that the release of a drug such as salicylic acid, from o/w emulsions is governed by transfer from the oil phase. Since the calculated slopes were smaller in the case of the concentrated emulsions when compared with release from the oily solution, the rate-determining step seems to be the transfer of salicylic acid across the oil/water interface. Therefore, these results also suggest that the properties of the interfacial film do not change considerably, e.g. the film does not become more condensed or multilayered, in spite of the increased cetomacrogol concentration. However, due to the slow release and the complexity of the emulsified systems, further interpretation of release mechanism was not possible.

5.3.4.4.2 Effect of pH on drug release from emulsions

To determine if it is possible to influence the release of drug from these emulsions by changing the pH of the receptor solution, drug release experiments were performed with 4 McIlvane buffer solutions of pH 2.2, 3.0, 5.0 and 7.0 whose ionic strength had been adjusted to 0.5 with KCl. The results of these release experiments a week after preparation of the emulsions are given in Figures 5.15-5.23 and the slopes of the lines are summarized in Tables 5.11-5.19. The effect of pH on release rate was similar to that found in the previous chapter: an increase in pH resulted in an increased release rate. However, unlike constant release rate from emulsions to water, every emulsion showed different release rates to buffer solutions as shown in Figure 5.24.

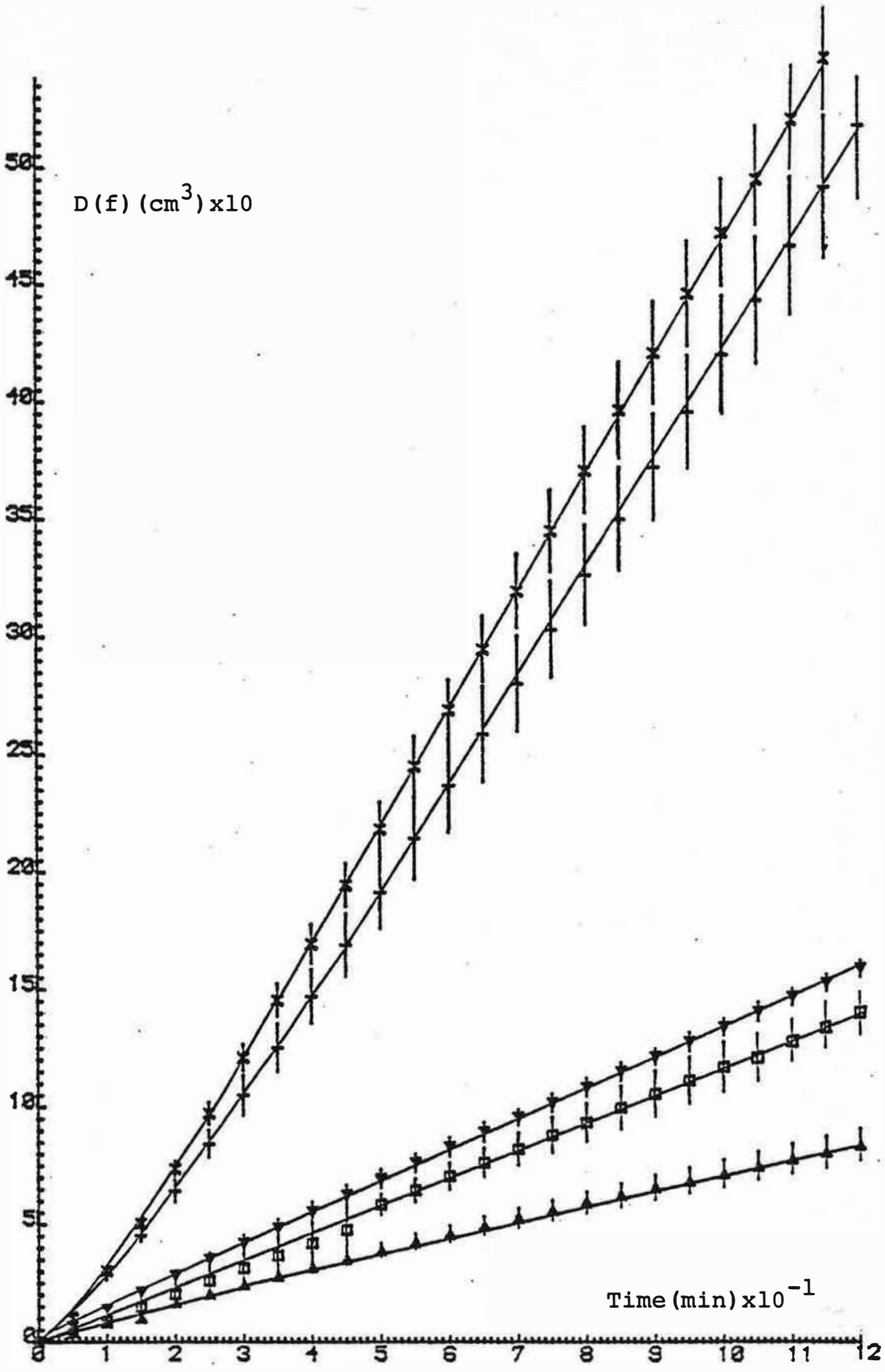


Figure 5.15. Effect of pH on salicylic acid release from Emulsion II-1. (▲) pH 2.2, (▼) pH 3.0, (+) pH 5.0, (×) pH 7.0, (□) distilled water.

Table 5.11. Effect of pH and the ageing on drug release from Emulsion II-1.

Age	Receptor solution pH	Slope $cm^3\ min^{-1}$	Correlation coefficient	Degrees of freedom
1 week	D. water	0.0115	0.9927	74
	2.2	0.0068	0.9980	67
	3.0	0.0132	0.9974	90
	5.0	0.0447	0.9930	90
	7.0	0.0513	0.9898	74
6 weeks	D. water	0.0112	0.9926	70
	2.2	0.0068	0.9980	67
	3.0	0.0128	0.9929	49
	5.0	0.0430	0.9961	55
	7.0	0.0503	0.9898	74
3 months	D. water	0.0113	0.9980	67
	2.2	0.0069	0.9958	90
	3.0	0.0125	0.9904	67
	5.0	0.0427	0.9994	55
	7.0	0.0491	0.9992	55
6 months	D. water	0.0114	0.9997	82
	2.2	0.0068	0.9993	74
	3.0	0.0125	0.9989	74
	5.0	0.0425	0.9993	74
	7.0	0.0497	0.9985	74

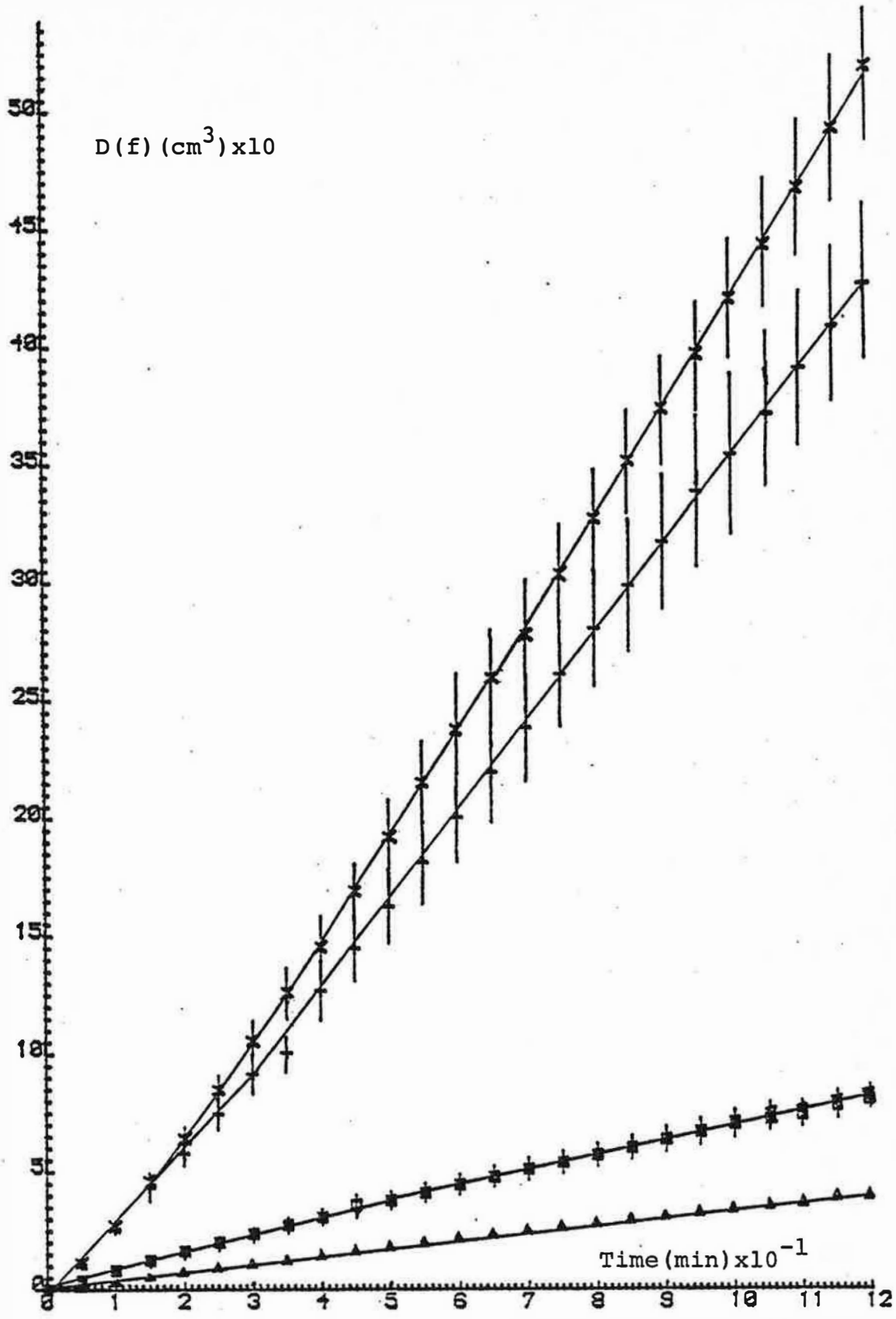


Figure 5.16. Effect of pH on salicylic acid release from Emulsion II-2. (▲) pH 2.2, (▼) pH 3.0, (+) pH 5.0, (×) pH 7.0, (□) distilled water.

Table 5.12. Effect of pH and the ageing on drug release from Emulsion II-2.

Age	Receptor solution pH	Slope $cm^3\ min^{-1}$	Correlation coefficient	Degrees of freedom
1 week	D. water	0.0072	0.9935	90
	2.2	0.0039	0.9989	74
	3.0	0.0070	0.9920	74
	5.0	0.0371	0.9856	74
	7.0	0.0448	0.9953	74
6 weeks	D. water	0.0072	0.9985	90
	2.2	0.0035	0.9976	55
	3.0	0.0071	0.9899	74
	5.0	0.0367	0.9932	55
	7.0	0.0445	0.9978	52
3 months	D. water	0.0069	0.9994	67
	2.2	0.0038	0.9885	74
	3.0	0.0069	0.9985	74
	5.0	0.0363	0.9936	55
	7.0	0.443	0.9919	66
6 months	D. water	0.0066	0.9929	103
	2.2	0.0037	0.9985	74
	3.0	0.0065	0.9993	74
	5.0	0.0365	0.9987	74
	7.0	0.0449	0.9935	74

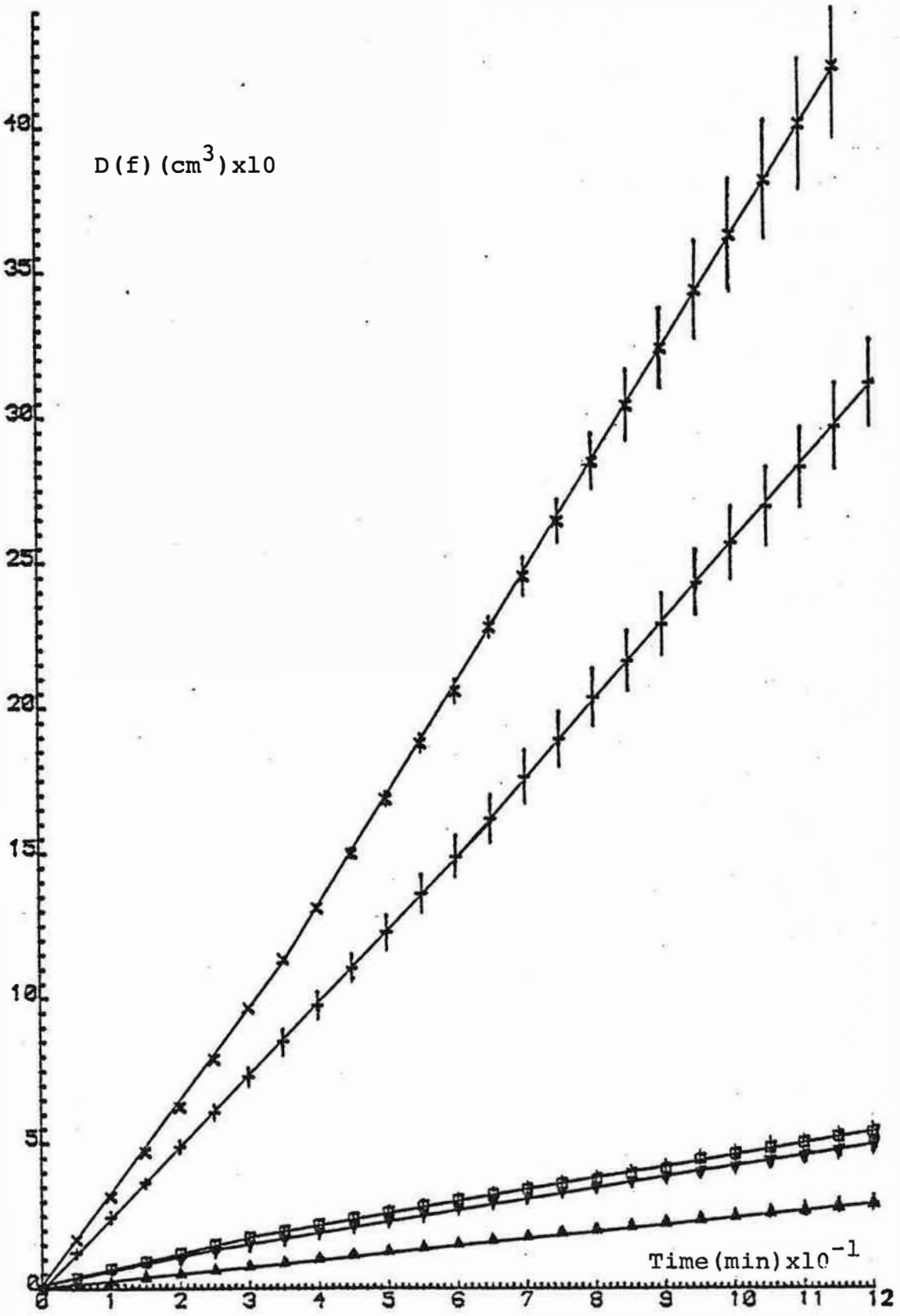


Figure 5.17. Effect of pH on salicylic acid release from Emulsion II-3. (▲) pH 2.2, (▼) pH 3.0, (+) pH 5.0, (×) pH 7.0, (□) distilled water.

Table 5.13. Effect of pH and the ageing on drug release from Emulsion II-3.

Age	Receptor solution pH	Slope $cm^3\ min^{-1}$	Correlation coefficient	Degrees of freedom
1 week	D. water	0.0045	0.9726	43
	2.2	0.0024	0.9896	90
	3.0	0.0040	0.9935	74
	5.0	0.0261	0.9962	67
	7.0	0.0376	0.9958	90
6 weeks	D. water	0.0042	0.9929	49
	2.2	0.0026	0.9416	49
	3.0	0.0044	0.9618	49
	5.0	0.0246	0.9926	90
	7.0	0.0372	0.9929	90
3 months	D. water	0.0043	0.9975	66
	2.2	0.0026	0.9862	34
	3.0	0.0043	0.9879	49
	5.0	0.0233	0.9946	49
	7.0	0.0372	0.9866	66
6 months	D. water	0.0045	0.9893	55
	2.2	0.0024	0.9930	90
	3.0	0.0043	0.9989	74
	5.0	0.0245	0.9987	67
	7.0	0.0369	0.9935	67

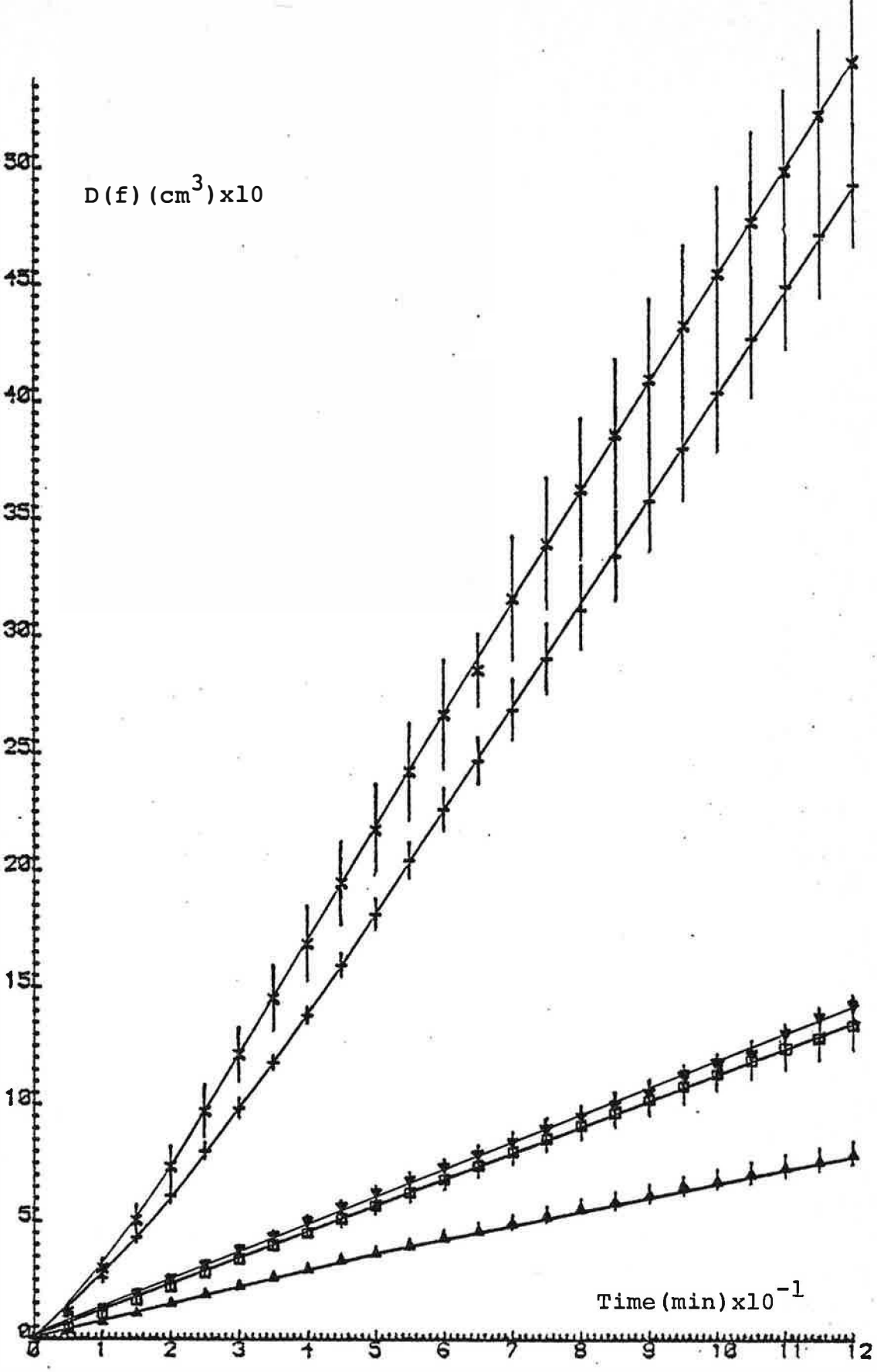


Figure 5.18. Effect of pH on salicylic acid release from Emulsion II-4. (▲) pH 2.2, (▼) pH 3.0, (+) pH 5.0, (×) pH 7.0, (□) distilled water.

Table 5.14. Effect of pH and the ageing on drug release from Emulsion II-4.

Age	Receptor solution pH	Slope $cm^3\ min^{-1}$	Correlation coefficient	Degrees of freedom
1 week	D. water	0.0113	0.9910	90
	2.2	0.0064	0.9911	90
	3.0	0.0114	0.9932	74
	5.0	0.0431	0.9949	90
	7.0	0.0478	0.9900	55
6 weeks	D. water	0.0110	0.9932	55
	2.2	0.0063	0.9904	44
	3.0	0.0117	0.9989	44
	5.0	0.0425	0.9991	36
	7.0	0.0470	0.9998	36
3 months	D. water	0.0112	0.9939	66
	2.2	0.0064	0.9887	49
	3.0	0.0115	0.9972	49
	5.0	0.0420	0.9993	55
	7.0	0.0463	0.9985	55
6 months	D. water	0.0112	0.9899	55
	2.2	0.0062	0.9982	55
	3.0	0.0115	0.9885	55
	5.0	0.0421	0.9935	55
	7.0	0.0465	0.9972	55

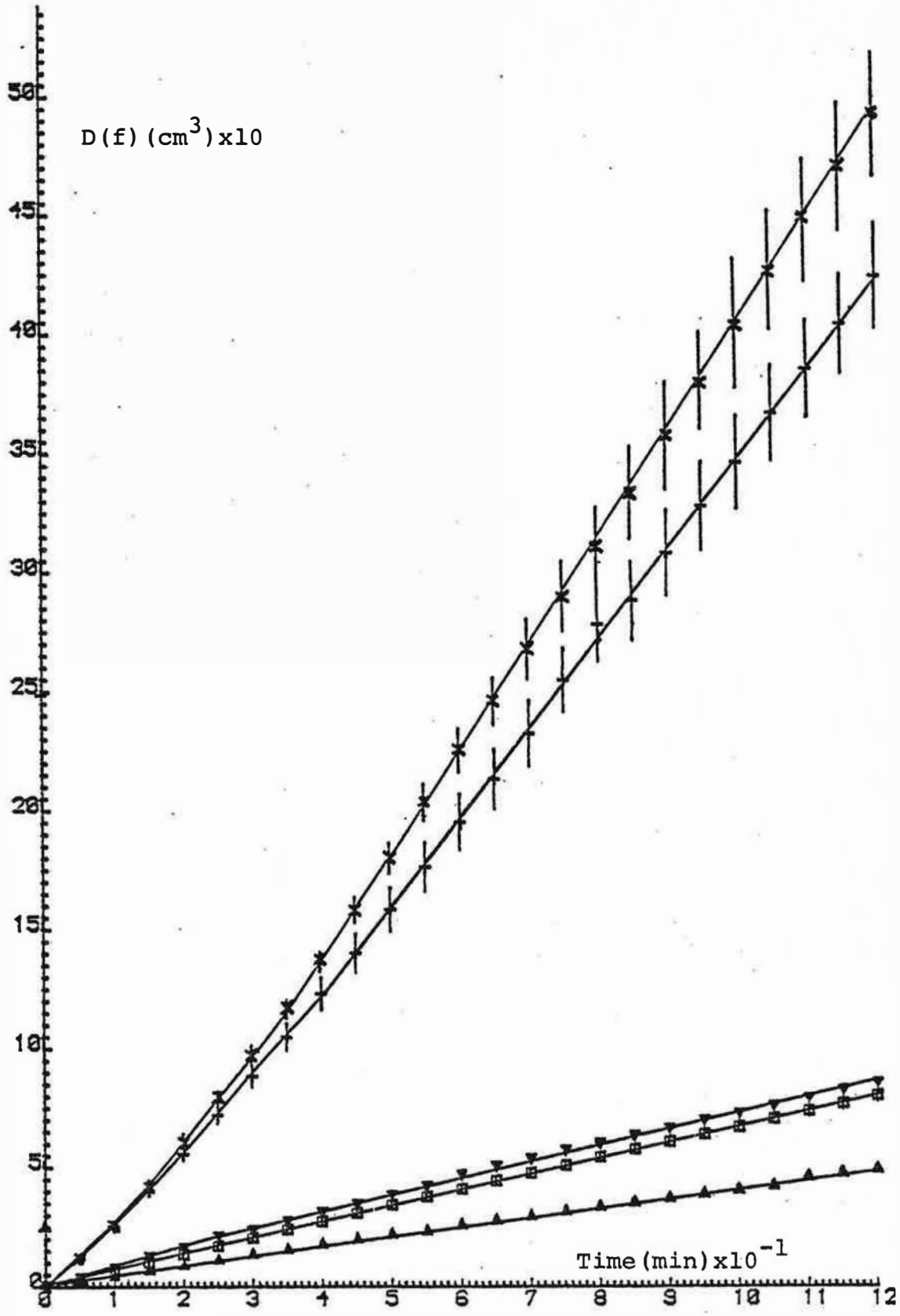


Figure 5.19. Effect of pH on salicylic acid release from Emulsion II-5. (▲) pH 2.2, (▼) pH 3.0, (+) pH 5.0, (×) pH 7.0, (□) distilled water.

Table 5.15. Effect of pH and the ageing on drug release from Emulsion II-5.

Age	Receptor solution pH	Slope $cm^3\ min^{-1}$	Correlation coefficient	Degrees of freedom
1 week	D. water	0.0070	0.9974	67
	2.2	0.0039	0.9955	57
	3.0	0.0070	0.9989	44
	5.0	0.0366	0.9950	89
	7.0	0.0431	0.9992	62
6 weeks	D. water	0.0070	0.9922	40
	2.2	0.0036	0.9900	55
	3.0	0.0072	0.9952	55
	5.0	0.0351	0.9962	55
	7.0	0.0433	0.9921	43
3 months	D. water	0.0065	0.9985	61
	2.2	0.0033	0.9974	61
	3.0	0.0070	0.9950	61
	5.0	0.0347	0.9962	61
	7.0	0.0430	0.9925	61
6 months	D. water	0.0063	0.9943	74
	2.2	0.0034	0.9989	67
	3.0	0.0069	0.9991	67
	5.0	0.0347	0.9963	67
	7.0	0.0432	0.9972	67

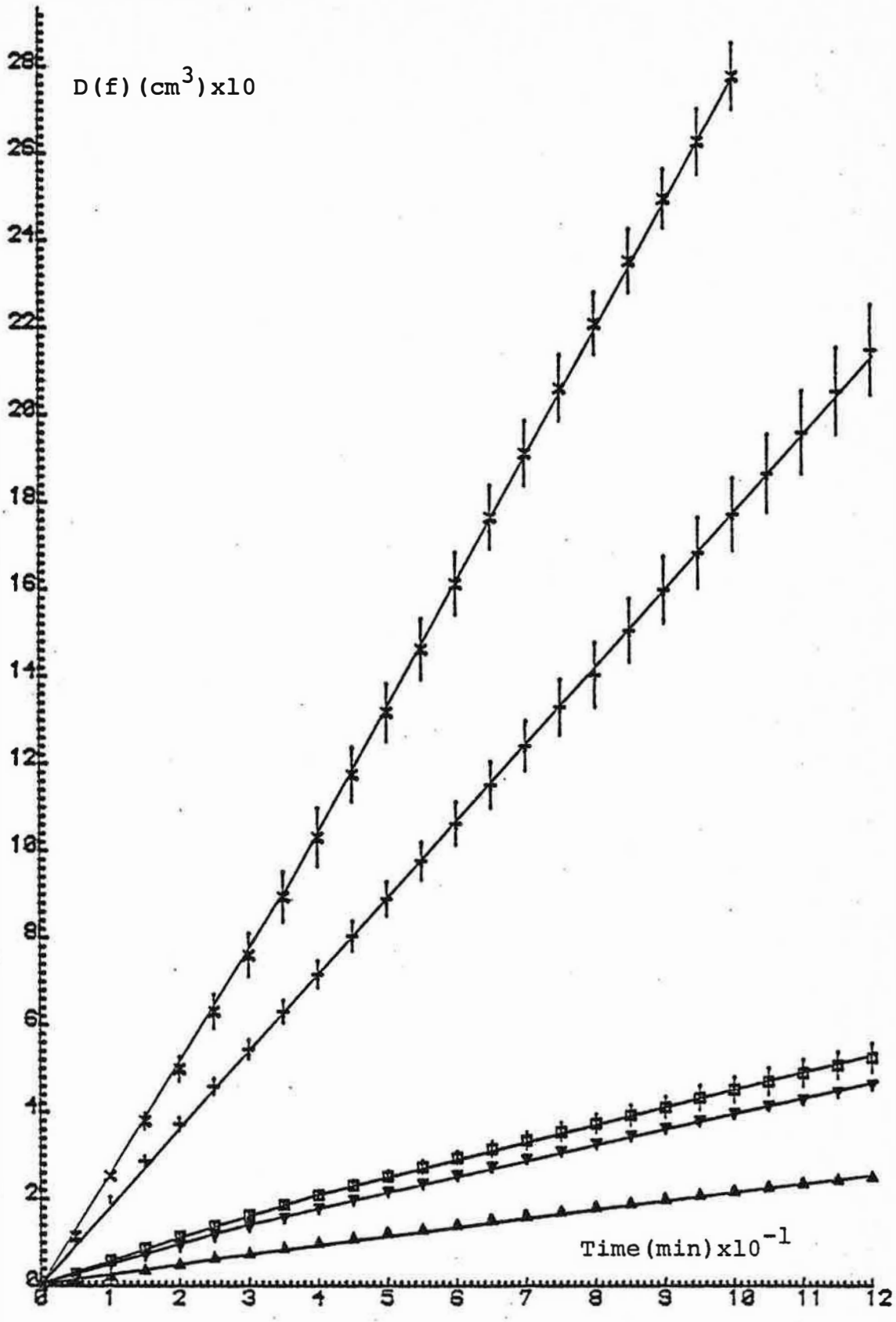


Figure 5.20. Effect of pH on salicylic acid release from Emulsion II-6. (▲) pH 2.2, (▼) pH 3.0, (+) pH 5.0, (×) pH 7.0, (□) distilled water.

Table 5.16. Effect of pH and the ageing on drug release from Emulsion II-6.

Age	Receptor solution pH	Slope $cm^3\ min^{-1}$	Correlation coefficient	Degrees of freedom
1 week	D. water	0.0044	0.9933	44
	2.2	0.0020	0.9977	90
	3.0	0.0037	0.9987	90
	5.0	0.0176	0.9962	67
	7.0	0.0287	0.9981	67
6 weeks	D. water	0.0043	0.9973	67
	2.2	0.0019	0.9987	67
	3.0	0.0036	0.9973	67
	5.0	0.0169	0.9962	67
	7.0	0.0290	0.9953	67
3 months	D. water	0.0046	0.9273	34
	2.2	0.0019	0.9947	44
	3.0	0.0036	0.9959	44
	5.0	0.0172	0.9983	44
	7.0	0.0285	0.9991	44
6 months	D. water	0.0044	0.9647	72
	2.2	0.0017	0.9957	46
	3.0	0.0035	0.9943	46
	5.0	0.0165	0.9973	35
	7.0	0.0283	0.9825	46

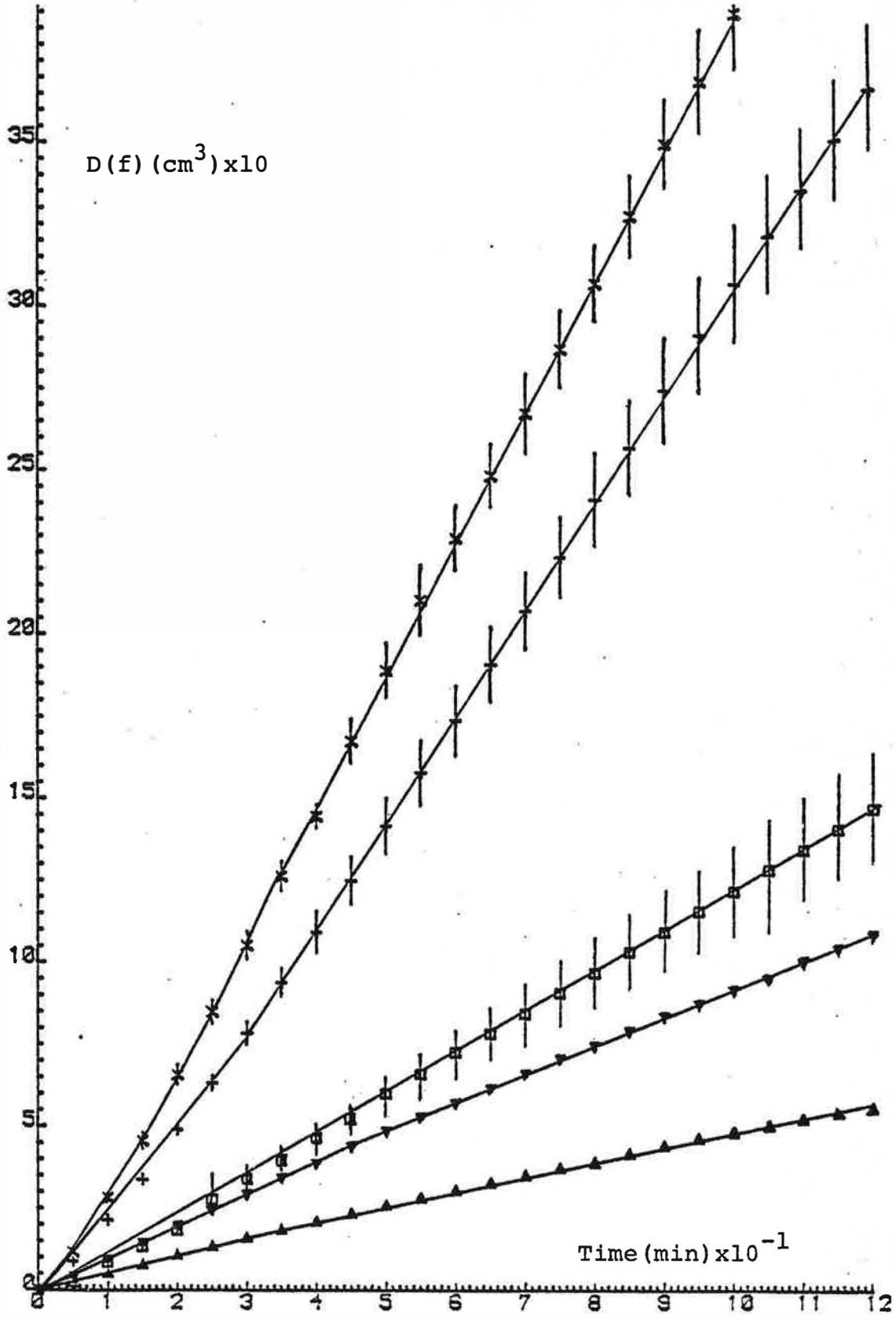


Figure 5.21. Effect of pH on salicylic acid release from Emulsion II-7. (▲) pH 2.2, (▼) pH 3.0, (+) pH 5.0, (×) pH 7.0, (□) distilled water.

Table 5.17. Effect of pH and the ageing on drug release from Emulsion II-7.

Age	Receptor solution pH	Slope $cm^3\ min^{-1}$	Correlation coefficient	Degrees of freedom
1 week	D. water	0.0096	0.9960	90
	2.2	0.0050	0.9977	55
	3.0	0.0091	0.9995	55
	5.0	0.0321	0.9949	55
	7.0	0.0403	0.9973	55
6 weeks	D. water	0.0103	0.9909	55
	2.2	0.0051	0.9803	55
	3.0	0.0088	0.9915	55
	5.0	0.0309	0.9994	55
	7.0	0.0398	1.000	36
3 months	D. water	0.0102	0.9818	74
	2.2	0.0050	0.9909	74
	3.0	0.0085	0.9803	74
	5.0	0.0313	0.9917	74
	7.0	0.0387	0.9994	74
6 months	D. water	0.0102	0.9917	74
	2.2	0.0049	0.9923	74
	3.0	0.0082	0.9803	74
	5.0	0.0309	0.9858	74
	7.0	0.0385	0.9898	74

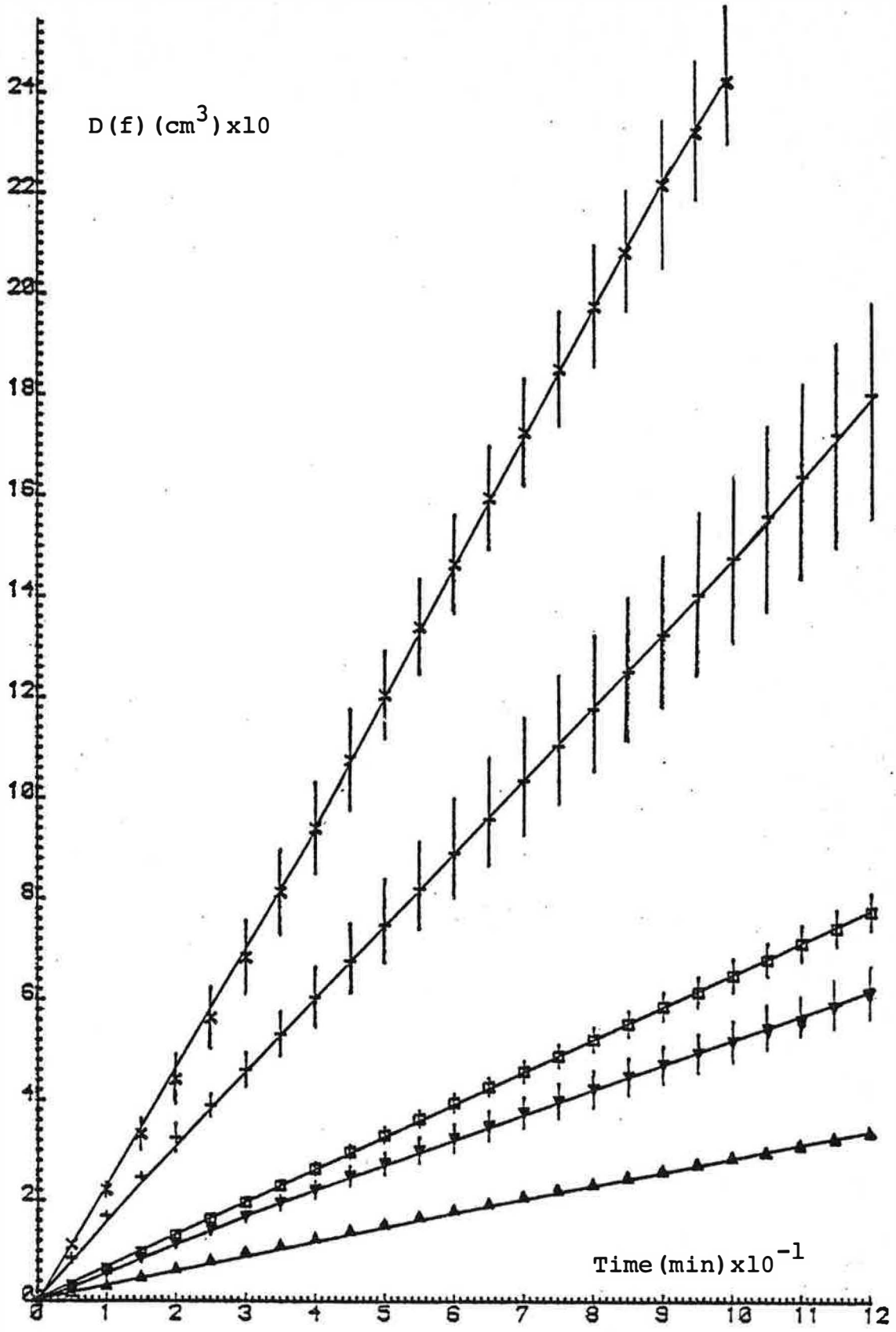


Figure 5.22. Effect of pH on salicylic acid release from Emulsion II-8. (▲) pH 2.2, (▼) pH 3.0, (+) pH 5.0, (×) pH 7.0, (□) distilled water.

Table 5.18. Effect of pH and the ageing on drug release from Emulsion II-8.

Age	Receptor solution pH	Slope $cm^3\ min^{-1}$	Correlation coefficient	Degrees of freedom
1 week	D. water	0.0069	0.9962	90
	2.2	0.0028	0.9969	74
	3.0	0.0051	0.9857	93
	5.0	0.0146	0.9557	90
	7.0	0.0254	0.9916	43
6 weeks	D. water	0.0068	0.9928	67
	2.2	0.0026	0.9817	55
	3.0	0.0045	0.9952	61
	5.0	0.0139	0.9657	55
	7.0	0.0253	0.9958	61
3 months	D. water	0.0069	0.9972	55
	2.2	0.0026	0.9817	55
	3.0	0.0047	0.9958	55
	5.0	0.0140	0.9997	55
	7.0	0.0252	0.9916	55
6 months	D. water	0.0067	0.9962	55
	2.2	0.0016	0.9857	55
	3.0	0.0047	0.9597	55
	5.0	0.0141	0.9647	55
	7.0	0.0247	0.9849	55

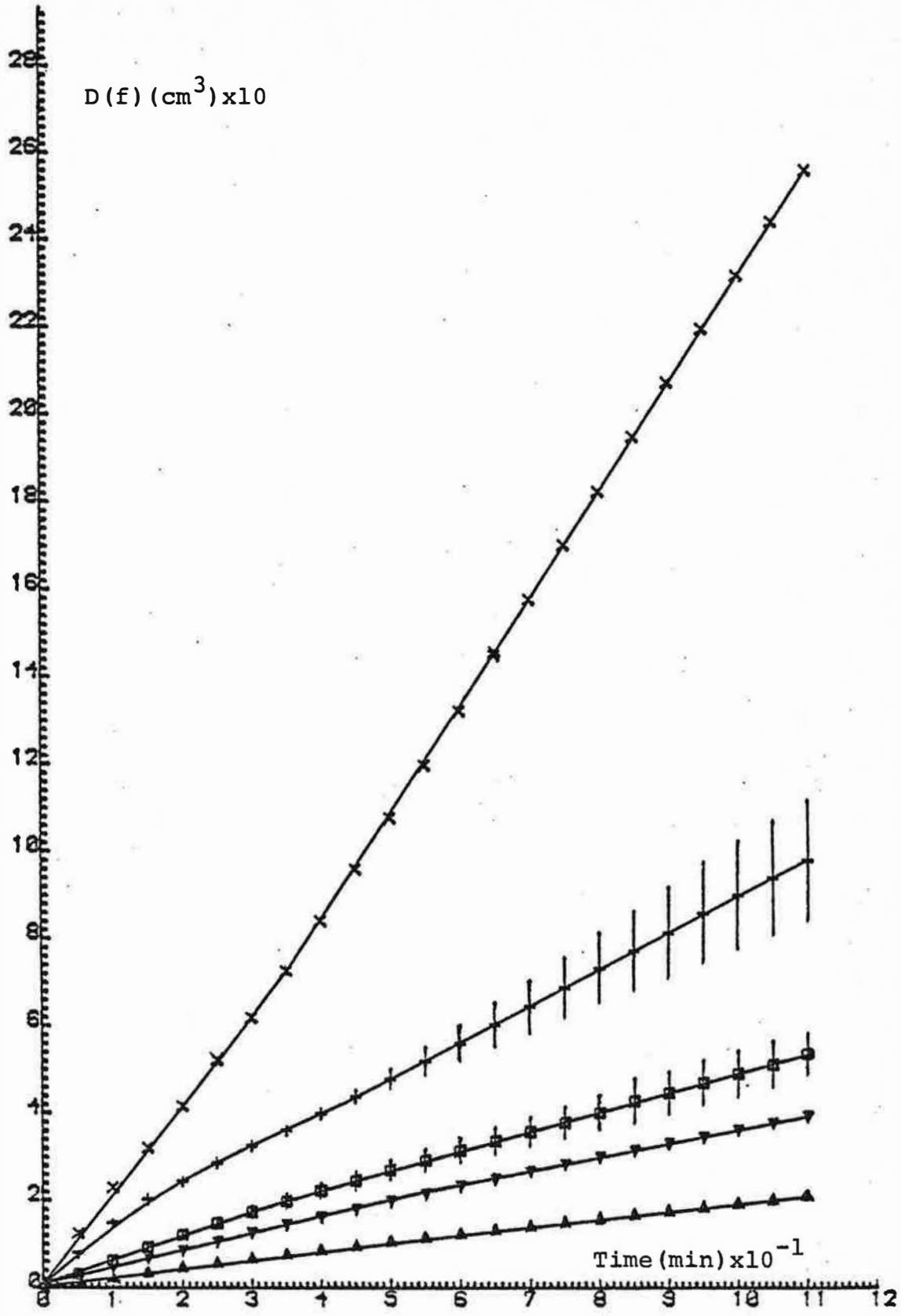


Figure 5.23. Effect of pH on salicylic acid release from Emulsion II-9. (▲) pH 2.2, (▼) pH 3.0, (+) pH 5.0, (×) pH 7.0, (□) distilled water.

Table 5.19. Effect of pH and the ageing on drug release from Emulsion II-9.

Age	Receptor solution pH	Slope $cm^3\ min^{-1}$	Correlation coefficient	Degrees of freedom
1 week	D. water	0.0045	0.9793	90
	2.2	0.0018	0.9923	61
	3.0	0.0034	0.9991	82
	5.0	0.0082	0.9713	82
	7.0	0.0206	0.9968	82
6 weeks	D. water	0.0040	0.9968	90
	2.2	0.0019	0.9926	90
	3.0	0.0038	0.9921	90
	5.0	0.0081	0.9749	90
	7.0	0.0206	0.9897	90
3 months	D. water	0.0040	0.9973	90
	2.2	0.0018	0.9973	90
	3.0	0.0039	0.9879	90
	5.0	0.0079	0.9753	90
	7.0	0.0203	0.9873	90
6 months	D. water	0.0038	0.9735	90
	2.2	0.0017	0.9879	90
	3.0	0.0035	0.9898	90
	5.0	0.0074	0.9898	90
	7.0	0.0200	0.9843	90

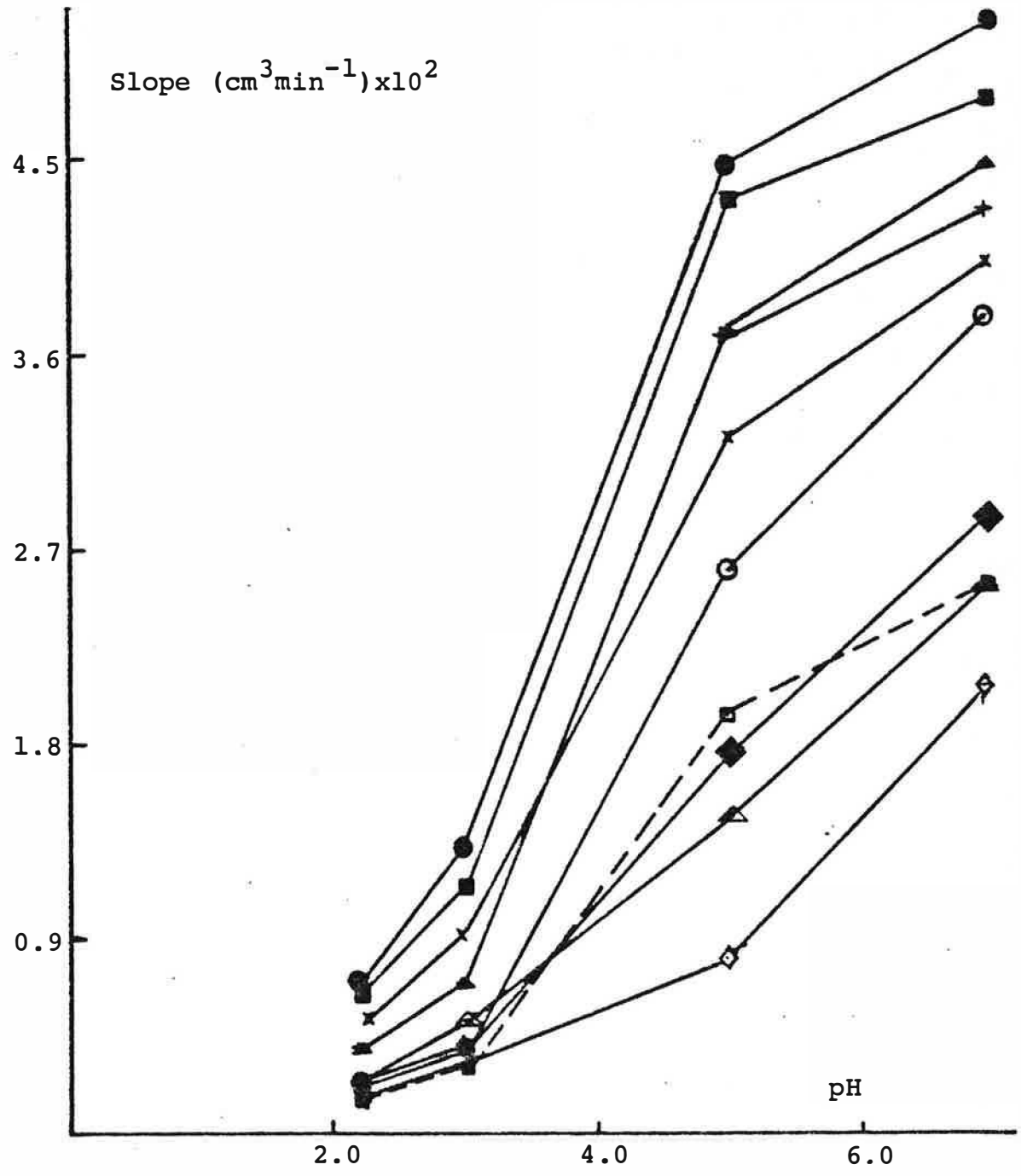


Figure 5.24. Effect of pH on salicylic acid release from emulsions, (●) II-1, (▲) II-2, (○) II-3, (■) II-4, (+) II-5, (◆) II-6, (x) II-7, (△) II-8, (◇) II-9, and (□) Miglyol.

This may suggest that not only the oil phase but also the aqueous and micellar phases of the emulsions contribute to the release. Complexity of these systems does not allow further definite interpretation of release mechanism. However, one may conclude that, in general, increasing the oil and surfactant concentrations result in a decreased release rate due to a greater amount of salicylic acid held in the oil and micellar phases. Depending upon the pH of the receptor solution, the rate of salicylic acid transport from both the oil and the micellar phases might have changed and this resulted in varying overall release rates from the emulsions. However, when the effect of pH on salicylic acid release from Miglyol was studied (Figure 5.25, Table 5.20), faster release was observed than from some of the emulsions, especially the concentrated ones (Figure 5.24). As discussed previously, this can again be an indication of the existence of an interfacial film which acts as a barrier to drug transport from the oil phase producing the rate-limiting step in drug release. Thus, the reduction of the drug concentration in the oil phases of the emulsions due to the partitioning in the aqueous and micellar phases may be the reason for the slower release from the emulsions having the same oil/water volume ratios.

In order to investigate further whether the properties of the interfacial film changed with increasing cetomacrogol concentrations, some interfacial tension measurements were performed. The pendant drop method was used to calculate the interfacial tensions as described elsewhere (Stauffer, 1965; Fordham, 1948). A projected image of the drop,

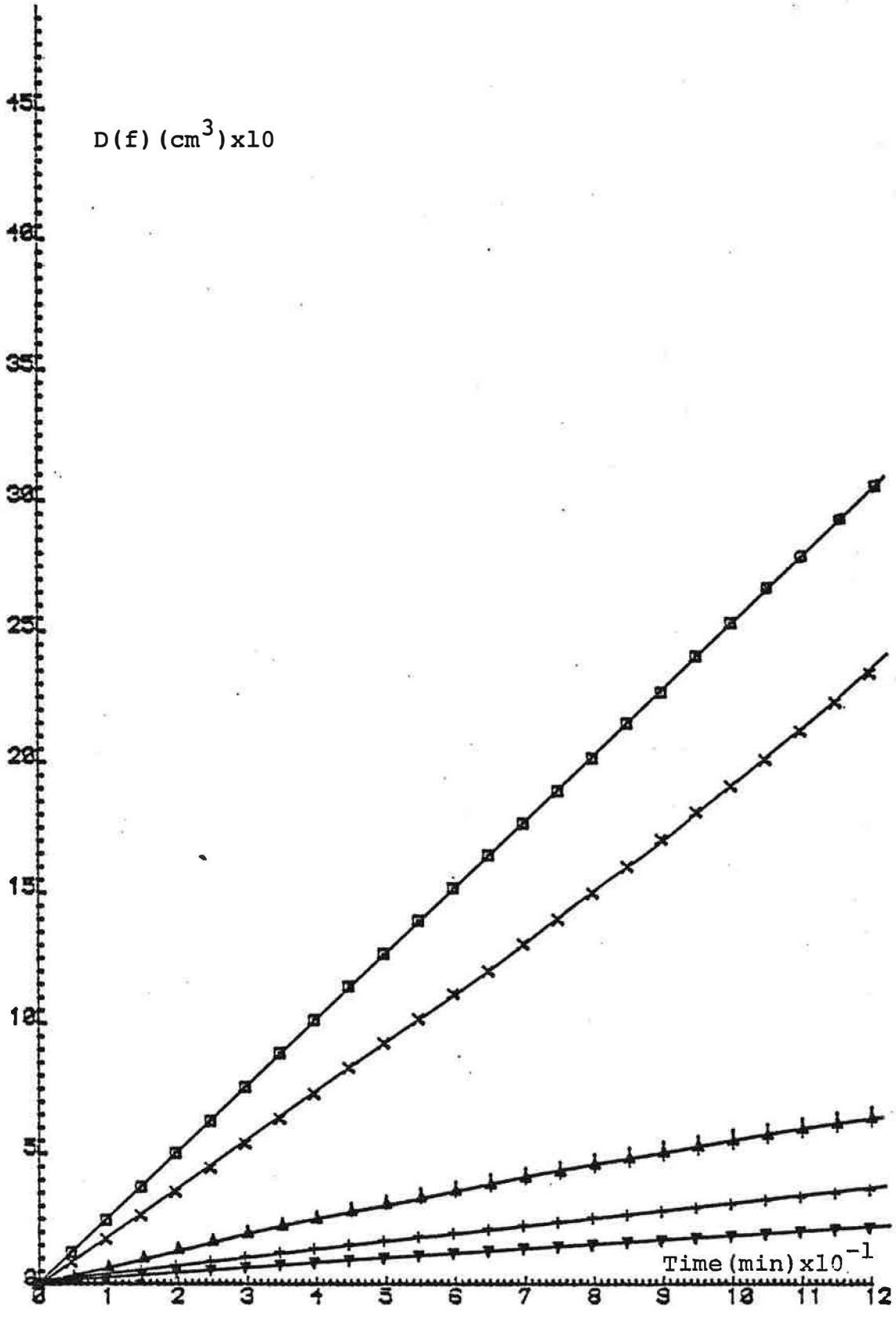


Figure 5.25. Effect of pH on salicylic acid release from Miglyol. (▼) pH 2.2, (+) pH 3.0, (x) pH 5.0, (□) pH 7.0, (▲) distilled water.

Table 5.20. The effect of pH on salicylic acid release from Miglyol. Drug concentration is 0.1% w/v.

Receptor solution	Slope $cm^3\ min^{-1}$	Correlation coefficient	Degrees of freedom
D. water	0.0052	0.9967	67
2.2	0.0018	0.9991	44
3.0	0.0030	0.9993	44
5.0	0.0196	0.9997	44
7.0	0.0253	1.000	55

which was formed in a Perspex cell containing Miglyol at 25°C±0.2°C was used to measure the maximum diameter d_e and the d_s at a horizontal plane distant d_e from the bottom of the drop and these were used for the calculations. The results are given in Table 5.21 and indicate that:

(a) Cetomacrogol-1000 did not reduce the interfacial tension between Miglyol and water very much, even the emulsions were very stable;

(b) further increase in the concentration of the surfactant did not influence the interfacial tension supporting the view that there was no structural change in the interfacial film, and

(c) with the presence of salicylic acid in Miglyol, there was no significant change in interfacial tension.

Thus, it is apparent that no complexation occurs between salicylic acid and cetomacrogol-1000 as suggested in 5.3.4.1 and 5.3.4.2.

From all of the above, one can suggest that the release of salicylic acid from the emulsions is governed by transfer from the oil phase and the extent of the distribution of the drug in various phases affects it considerably. The release is slower the bigger the phase volume ratio or for the same volume ratio the higher the micellar phase concentration.

5.3.4.4.3 The effect of ageing on drug release from emulsions

In order to demonstrate the effect of ageing, in other words the stability of the emulsions, on the drug release the experiments were performed after 6 weeks, 3 months and 6 months together with the long term and the accelerated

Table 5.21. Effect of cetomacrogol concentration on interfacial tension between water and Miglyol 812 in the absence and presence of salicylic acid at 25°C. Salicylic acid concentration in the oil phase is 0.10% w/v.

% w/v cetomacrogol in aqueous phase	Interfacial tension (dynes. cm^{-1}) mean ± SD	Number of droplets
0.25	6.34±0.039	8
0.25	6.34±0.294	12
0.50	6.51±0.168	8
0.67	6.25±0.426	6
1.00	6.52±0.320	9
1.00	6.14±0.363	7
2.00	6.00±0.223	8
2.00	6.06±0.377	7

stability test. The stability tests and the results will be discussed in Chapter 6. In this part of the thesis, only the effect of ageing on drug release will be discussed.

Since the release to higher pH buffer solutions was thought to be more sensitive, it was decided that experiments which were carried out a week after the preparation of the emulsions, should be repeated for up to 6 months in order to determine the effect of ageing. There was no change observed in the shape of the curves, which were similar to those shown in Figures 5.15-5.23 and the slopes of these are included in Tables 5.11-5.19. However, although most of the emulsions showed slightly slower release, the differences were not very significant. Therefore, it was concluded that ageing did not influence the release characteristics of the emulsions to any significant extent.

5.3.5 Effect of the nature of the surfactant on salicylic acid release from emulsions

Since it was concluded that the increasing amount of cetomacrogol did not affect the properties of the interfacial film, it was decided to use different surfactants in order to evaluate the effect of the interfacial film on drug release. The oil/water ratio, ϕ, and the concentration of the surfactants were kept constant at 50/50 and 1% w/v. The surfactants used were sodium lauryl sulphate (SLS), cetrimide (CTAB), and Tween 20 and Span 80 mixtures to give different HLB values. The emulsions were prepared as described in Chapter 2 and the salicylic acid concentration was always kept at 0.1% w/v, the receptor being distilled

water. The composition of the emulsions is given in Table 5.22.

Release experiments were conducted one day after preparation and a water-Miglyol mixture containing no surfactant was used as a control. As expected, this 50/50 Miglyol/water mixture immediately formed two layers in the donor cell despite vigorous mixing before it was introduced into the cell, but despite it not having a large interfacial area, it was thought that the results might be compared with the release characteristics of the emulsions under investigation. Control solutions of some surfactant/water and surfactant/Miglyol solutions were also tested together with the emulsions and the calculated slopes are summarized in Table 5.23.

As can be seen from Table 5.23, release from Emulsion III-1 and its control solutions was extremely slow. This was due mainly to the anionic drug-cationic surfactant interaction. The complex did not diffuse out of the solution. Although it was thought unnecessary to investigate further the extent of the interaction between salicylic acid and CTAB; however, for the sake of completeness, salicylic acid release rates from the aqueous CTAB solutions at critical micellar concentration (CMC; 0.032%) and at ½ CMC (0.016%) were studied. The results (Table 5.24) clearly showed that even at submicellar concentration, CTAB retarded the release due to the ionic interaction. Thus the release characteristics of Emulsion III-1 will not be included in the discussion.

Table 5.22. Composition of the emulsions prepared with different surfactants.

Emulsion	Surfactant	Ratio of Tween 20:Span 80 w:w	HLB
III-1	CTAB		
III-2	NLS		
III-3	Cetomacrogol-1000		
III-4	Tween 20/Span 80	5:0	16.7
III-5	"	4.5:0.5	15.46
III-6	"	4.0:1.0	14.22
III-7	"	3.0:2.0	11.74
III-8	"	2.0:3.0	9.26
III-9	"	1.0:4.0	6.78
III-10	"	0.5:4.5	5.54
III-11	"	0.0:5.0	4.30

Table 5.23. Effect of the nature of the surfactant on drug release from emulsions and control solutions.

Donor solution	Slope $cm^3\ min^{-1}$	Correlation coefficient	Degrees of freedom	K_{app}
Emulsion III-1	0.0005	0.9700	40	-
Emulsion III-2	0.0176	0.9961	90	3.76
Emulsion III-3	0.0050	0.9902	90	5.39
Miglyol/water:50/50	0.0058	0.9989	90	12.43
CTAB/water	0.0010	0.9626	55	
CTAB/Miglyol	0.0004	0.9986	44	
NLS/water	0.0498	0.9091	93	
NLS/Miglyol	0.0102	0.9944	90	
Cetomacrogol/water	0.0319	0.9558	74	
Cetomacrogol/Miglyol	0.0055	0.9087	74	

Table 5.24. Effect of CTAB concentration on salicylic acid release from the aqueous solutions.

CTAB concentration % w/v	Slope $cm^3\ min^{-1}$	Correlation coefficient	Degrees of freedom
0.016	0.0505	0.9941	74
0.032	0.0429	0.9986	74
1.000	0.0010	0.9626	55

The other two emulsions, III-2 and III-3, and the control oil/water mixture showed different release patterns supporting the existence of the interfacial barrier and the importance of the surface area which is a result of the emulsification. In other words, Emulsion III-2 released the drug faster than the control mixture due to the increased surface area, and faster than Emulsion III-3 due to a weaker resistance of the SLS film. On the other hand, the release from Emulsion III-3 was the slowest due to the strong interfacial barrier to drug release in spite of the increased surface area.

When the emulsions of Tween 20/Span 80 were tested, different rates of release were observed. The calculated slopes are given in Table 5.25. The drug was released faster than the Miglyol/water mixture from each of these emulsions. When the slopes were plotted against the HLB of the surfactant mixture used to prepare the emulsion, an interesting relationship was observed. As shown in Figure 5.26, the drug release rate is minimal at an HLB range of about 10-13. These results again show the effect of the interfacial film on the globules on drug release. In the preparation of the emulsions, an emulsifier mixture combining a low HLB emulsifier with a high HLB one usually yields a more stable emulsion than does a single emulsifier (Akers and Lach, 1976; Takamura et al., 1979; Boyd et al., 1972) even if it gives the same HLB as the mixture. Takamura et al. (1979) reported that Tween 20/Span 80 mixtures give unstable liquid paraffin emulsions over the whole range of HLB values (4.3-16.9) studied. These

Table 5.25. Effect of HLB on salicylic acid release from the emulsions.

Emulsion No.	Slope $cm^3\ min^{-1}$	Correlation coefficient	Degress of freedom
III-4	0.0076	0.9981	90
III-5	0.0070	0.9998	90
III-6	0.0063	0.9967	82
III-7	0.0061	0.9997	66
III-8	0.0063	0.9916	66
III-9	0.0065	0.9916	90
III-10	0.0068	0.9963	90
III-11	0.0076	0.9910	74
Miglyol/water mixture	0.0058	0.9989	90

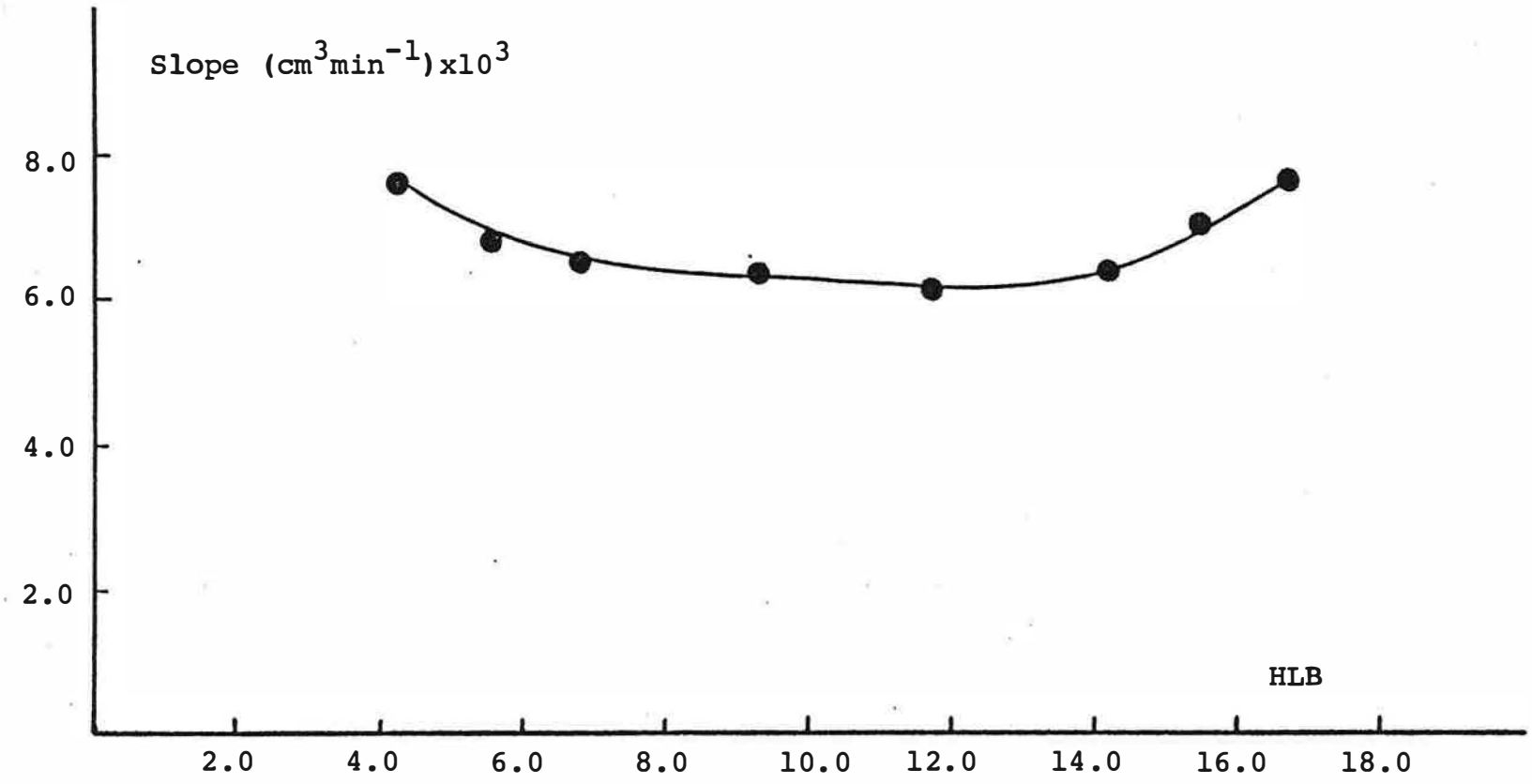


Figure 5.26. Effect of HLB of the surfactant mixture on drug release.

authors attributed this to the very large difference in HLB values (12.6) between Span 80 and Tween 20. In our studies, Span 80 alone did not stabilize the Miglyol emulsion (III-11) and a rather fast phase separation was observed. However, when the mixtures of Span 80 and Tween 20 were used, the stability of the emulsions was improved, especially around an HLB range of 10-13 where the release was the slowest. Although there was no visible separation with the HLB values higher than HLB = 11.74, the number of bigger globules in these emulsions increased indicating poorer emulsification. The presence of the bigger globules in the emulsions prepared with low and high HLB values was observed during the particle size analysis and the results will be reported later in Chapter 6. Although an emulsifier which is very effective in stabilizing an emulsion may be much less effective in facilitating the production of an initial small globule size and/or narrow globule size distribution (Boyd et al., 1972), in general emulsions having small globule size are thought to be more stable due to the faster creaming rate of the larger globules than smaller ones. Thus, the emulsions stabilized with Tween 20/Span 80 mixtures showing the smaller size distributions probably had a better coating of the globules and this affected their release properties. In order to further evaluate the properties of the interfacial films of the emulsions, some differential scanning calorimetry measurements were carried out with a Perkin Elmer DSC 2. Unfortunately no transition or inversion was observed between 20°-90°C, and above 90°C sharp changes on the thermograms were seen probably due to

the evaporation of the aqueous phases of the emulsions.

Lastly, interfacial tension measurements were conducted as described earlier (p. 166) in order to determine whether there was any relationship between this and the release properties of the emulsions. The results are listed in Table 5.26. Tween 20 was dissolved in water and Span 80 was dissolved in Miglyol and the concentrations of both surfactants were adjusted to resemble the amounts present in the aqueous and oil phases of the emulsions. As can be seen in Figure 5.27, the interfacial tension decreased with decreasing HLB and increased again when only Span 80 was present. The reduction in the interfacial tension to a low value does not always indicate a better stabilizing effect of the surfactant (Boyd et al., 1972), and as discussed before, cetomacrogol did not reduce the interfacial tension considerably between Miglyol and water, but stabilized the emulsions very efficiently. Similarly, Emulsion III-11 was not stable and separated in two days, although the interfacial tension was reduced to a lower value by Span 80 alone than by Tween 20 alone or some mixtures of these two surfactants (Figure 5.27). Furthermore, the emulsions prepared with 5.0 and 10.0% Span 80 did not show any better stability despite the further reduction in the interfacial tension (e.g. with 10% Span 80 in Table 5.26).

Different rates of Ephedrine release from emulsions stabilized with surfactant mixtures in the HLB range of 4.7 to 14.9 were reported by Waggoner et al. (1971). They concluded that the transport of the drug through the interface in an emulsion can be influenced by the HLB of

Table 5.26. Effect of Tween 20 and Span 80 on interfacial tension between water and Miglyol at 25°C.

HLB	Interfacial tension dynes cm^{-1} mean ± SD	Number of drops
16.7	4.56±0.122	9
15.46	3.22±0.426	8
14.22	2.09±0.283	10
11.74	0.86±0.215	15
9.26	0.53±0.075	27
6.78	0.39±0.053	33
5.54	0.32±0.022	5
4.3	1.27±0.205	9
16.7 (10% Tween 20)	3.34±0.128	8
4.3 (10% Span 80)	0.95±0.388	7
10.5 (10% Tween 20 + 10% Span 80)	0.15±0.033	6

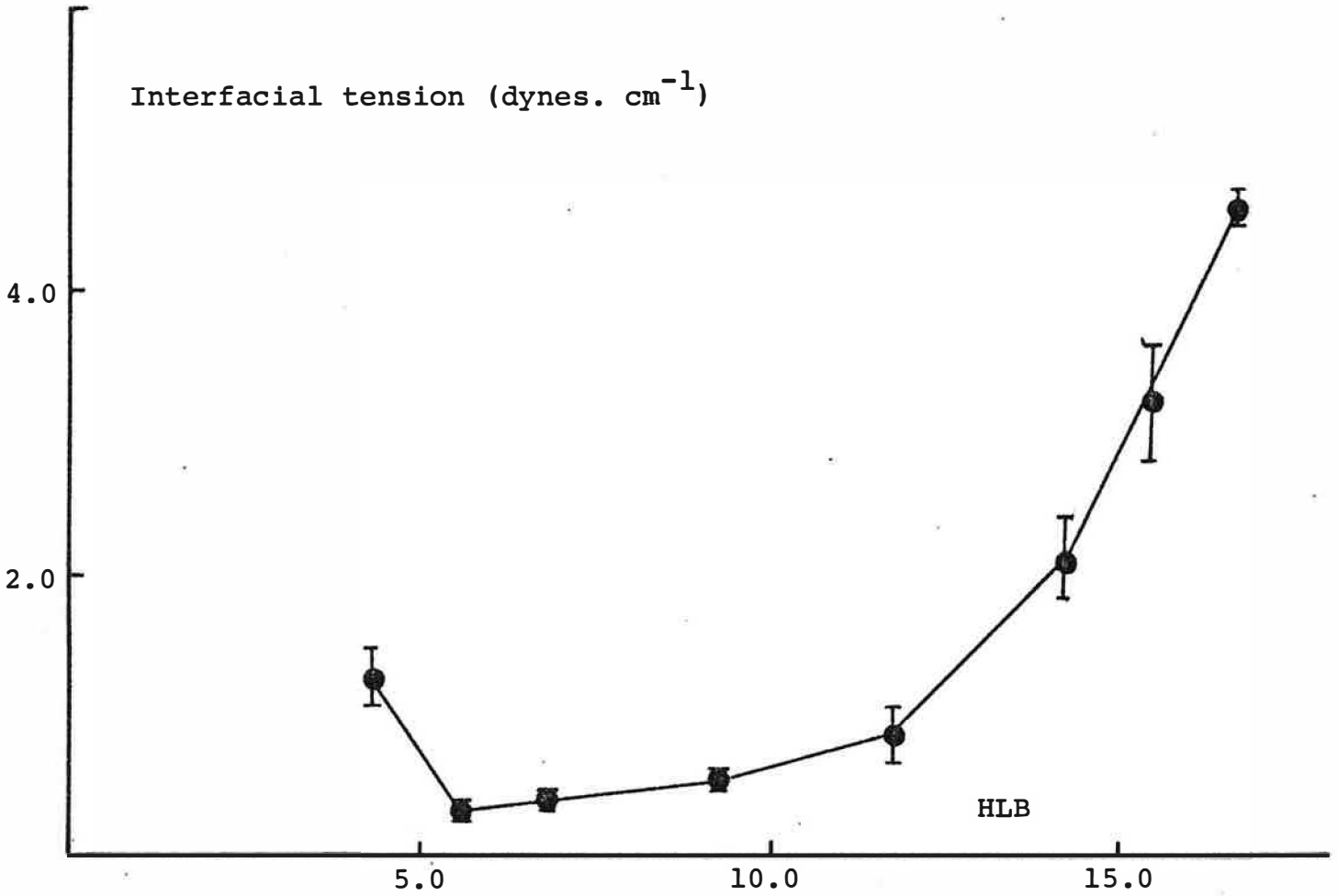


Figure 5.27. Effect of HLB on the interfacial tension between Miglyol and water.

the surfactants due to different arrangement and packing of the surfactants at the interface. In their studies they found the lowest release rates at HLB values of 9 and 10.

Lastly, three more emulsions were prepared with Tween 20/Span 80 mixture at a ratio of 4/1. The phase volume ratio and the salicylic acid concentrations were held constant as 50/50 and 0.10% w/v respectively and the concentration of the surfactant mixture was increased as given in Table 5.27. There was no difference in the microscopic appearances of the emulsions and no liquid crystals could be detected in any of them. The calculated slopes of the release curves given in Table 5.27 again suggest that release of salicylic acid is unaffected in the absence of a change in interfacial film on the globules.

5.3.6 Effect of the nature of the drug on drug release from emulsions

In order to determine the effect of the partition coefficient of a drug on its release from an emulsion, release experiments were performed on five different drugs incorporated in the same model emulsion. Although it is possible to change the apparent partition coefficient of a drug in an emulsified system by changing the concentration or the type of the surfactant and the oil phase, the true partition coefficient of a drug cannot be changed. Thus, the model drug, salicylic acid, alone could not reveal any true effect of partition coefficient on drug release. The emulsion used for this portion of the study was a cetomacrogol

Table 5.27. Effect of surfactant concentration on drug release.

Emulsion No.	Surfactant concentration % w/v	Slope $cm^3\ min^{-1}$	Correlation coefficient	Degrees of freedom
III-6	1	0.0063	0.9997	82
III-12	3	0.0061	0.9949	90
III-13	5	0.0063	0.9967	90

emulsion with a phase volume ratio of ϕ = 50/50 and the concentrations of the surfactant and the drugs were again kept constant at 1.0% w/v and 0.1% w/v respectively. For the control experiments the aqueous and oily solutions of the drugs were prepared as described before except for the oily solution of paracetamol which had a concentration of 0.05% w/v due to its low solubility. The equations for the calibration curves for each drug are given in Appendix II. The solubilities and the partition coefficients of these drugs at 37°C in the presence and absence of cetomacrogol were determined as described previously, the results being summarized in Table 5.28 together with the molecular weights of the drugs and the λ_{max} values used for their spectrophotometric analysis.

Figures 5.28-5.32 show the release curves of the drugs and their control solutions and the slopes of these curves are given in Table 5.29.

As shown in Figures 5.33 and 5.34, release from the emulsion and the oily solutions is an inverse function of the partition coefficient of the drugs studied. Benzoic acid and the molecules related to it showed a linear correlation between partition coefficient and the release from both the oily solution and the emulsions. Because in addition only paracetamol and phenacetin release from the emulsions and the oily solutions were studied, one cannot be sure if the linear relationship will hold for all analogues. However, these results clearly show that partition coefficient of a drug plays an important role in release and these two parameters are inversely related.

Table 5.28. Solubilities and partition coefficient of the drugs in the (a) absence and (b) presence of cetomacrogol.

Drug	MW	λ_{max} (μm)	Solubility at 37°C (g in 100 ml)		Partition coefficient at 37°C	
			a	b	a	b
Benzoic acid	122.12	227	0.488	0.848	10.196	5.260
3-OH Benzoic acid	138.12	288	1.345	1.449	0.937	0.481
Aspirin	180.20	297	3.403	9.181	5.587	4.752
Paracetamol	151.16	243	2.137	2.529	0.068	0.064
Phenacetin	179.21	245	1.267	2.148	4.172	2.639
Salicylic acid	138.12	297	0.338	0.805	12.430	5.391

Table 5.29. Release of various drugs from the emulsions and control solutions.

Donor / Drug	Water			Miglyol			Emulsion		
	Slope $cm^3 min^{-1}$	Correlation coefficient	DF	Slope $cm^3 min^{-1}$	Correlation coefficient	DF	Slope $cm^3 min^{-1}$	Correlation coefficient	DF
Benzoic acid	0.0503	0.9988	67	0.0059	0.9985	67	0.0078	0.9952	90
3-OH Benzoic acid	0.0495	0.9777	78	0.0125	0.9982	40	0.0229	0.9920	67
Aspirin	0.0362	0.9972	82	0.0104	0.9978	82	0.0156	0.9880	90
Paracetamol	0.0422	0.9973	19	0.0258	0.9920	82	0.0404	0.9969	58
Phenacetin	0.0411	0.9989	46	0.0081	0.9838	112	0.0112	0.9998	67
Salicylic acid	0.0560	0.9931	134	0.0052	0.9970	90	0.0050	0.9916	66

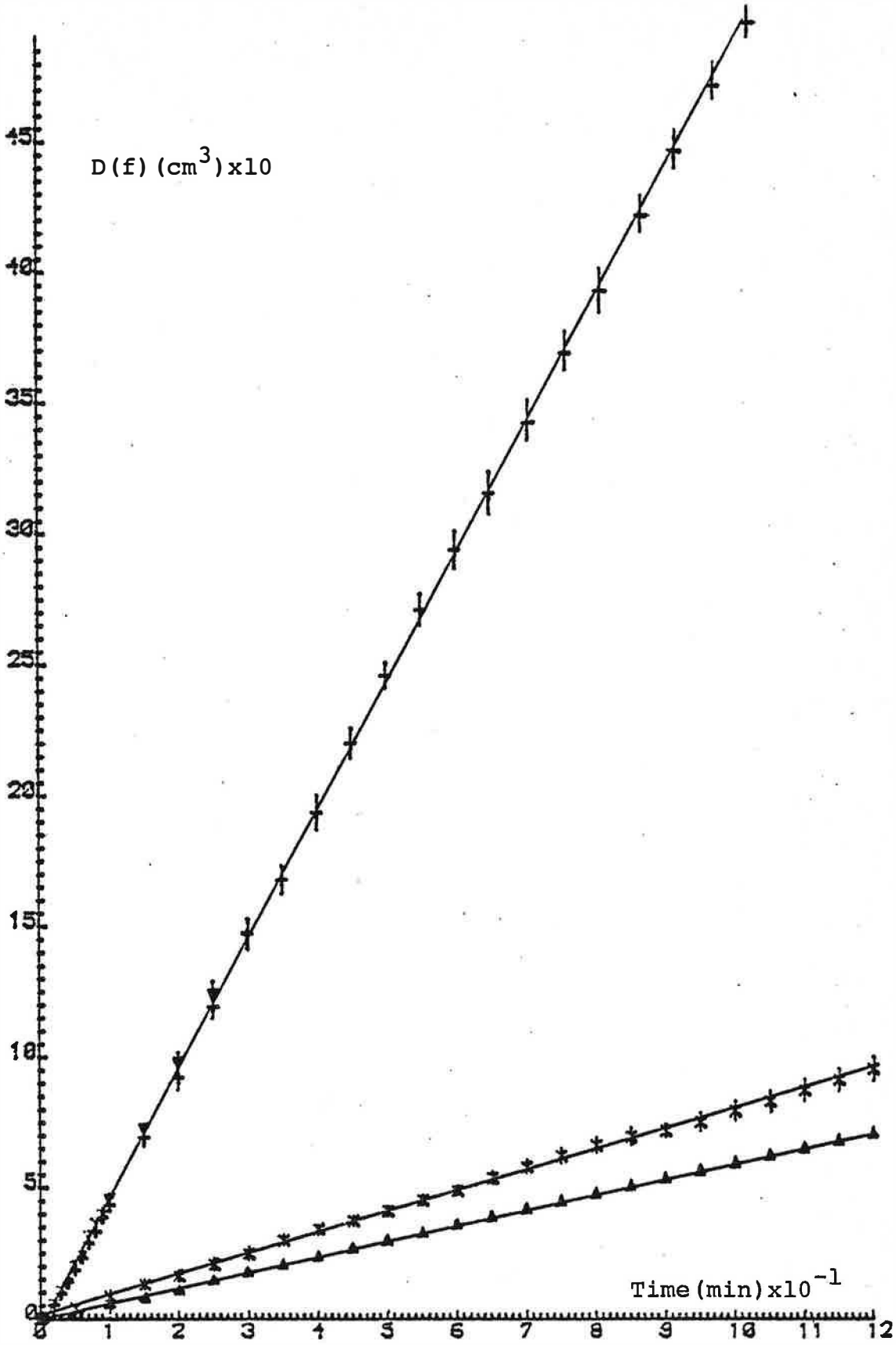


Figure 5.28. Benzoic acid release from (▲) Miglyol, (×) Emulsion, (▼) aqueous solution to 50 ml receptor solution, (+) aqueous solution to 100 ml receptor solution.

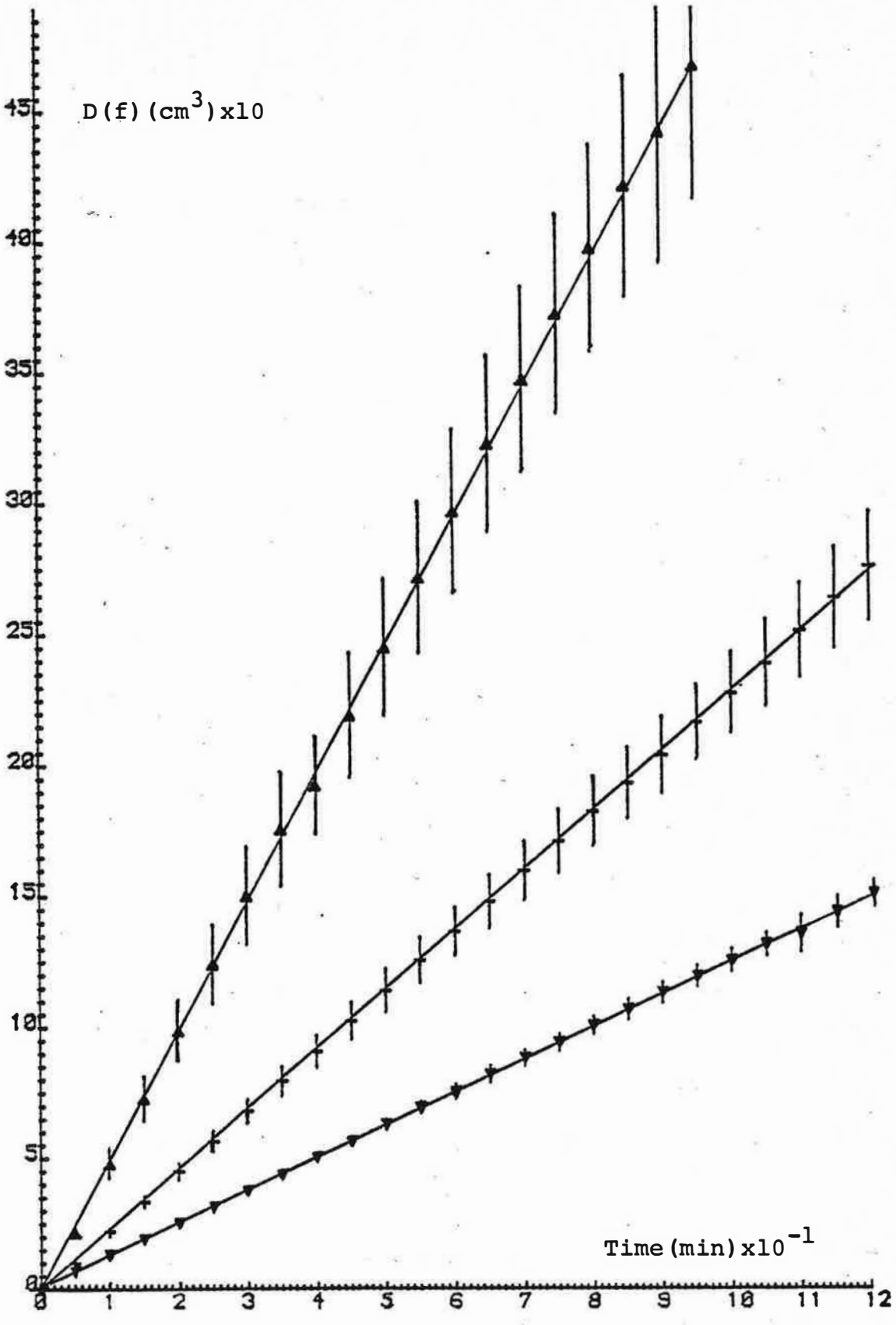


Figure 5.29. 3-hydroxy benzoic acid release from (▼) Miglyol, (+) Emulsion, (▲) aqueous solution.

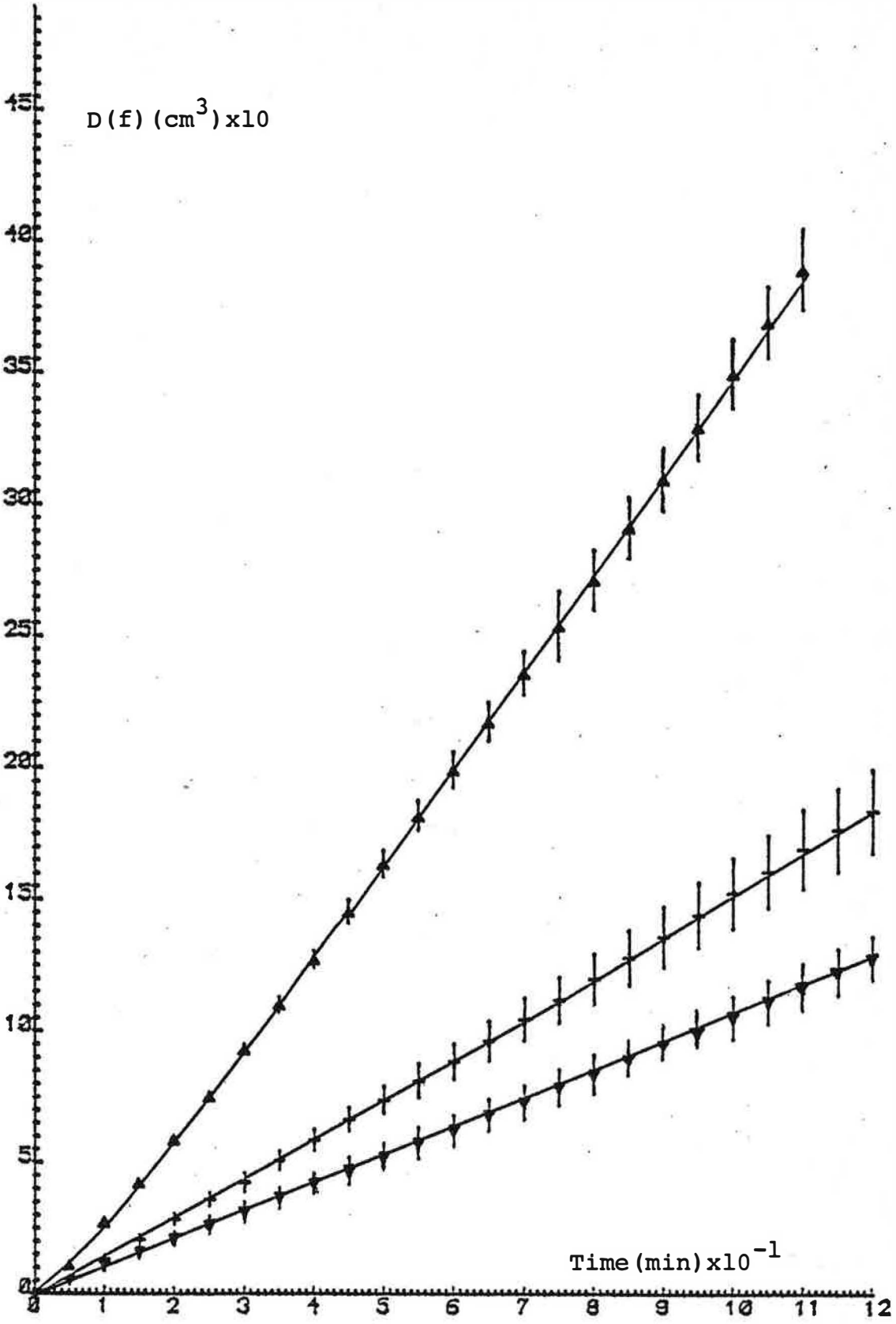


Figure 5.30. Aspirin release from (▼) Miglyol, (+) Emulsion, (▲) aqueous solution.

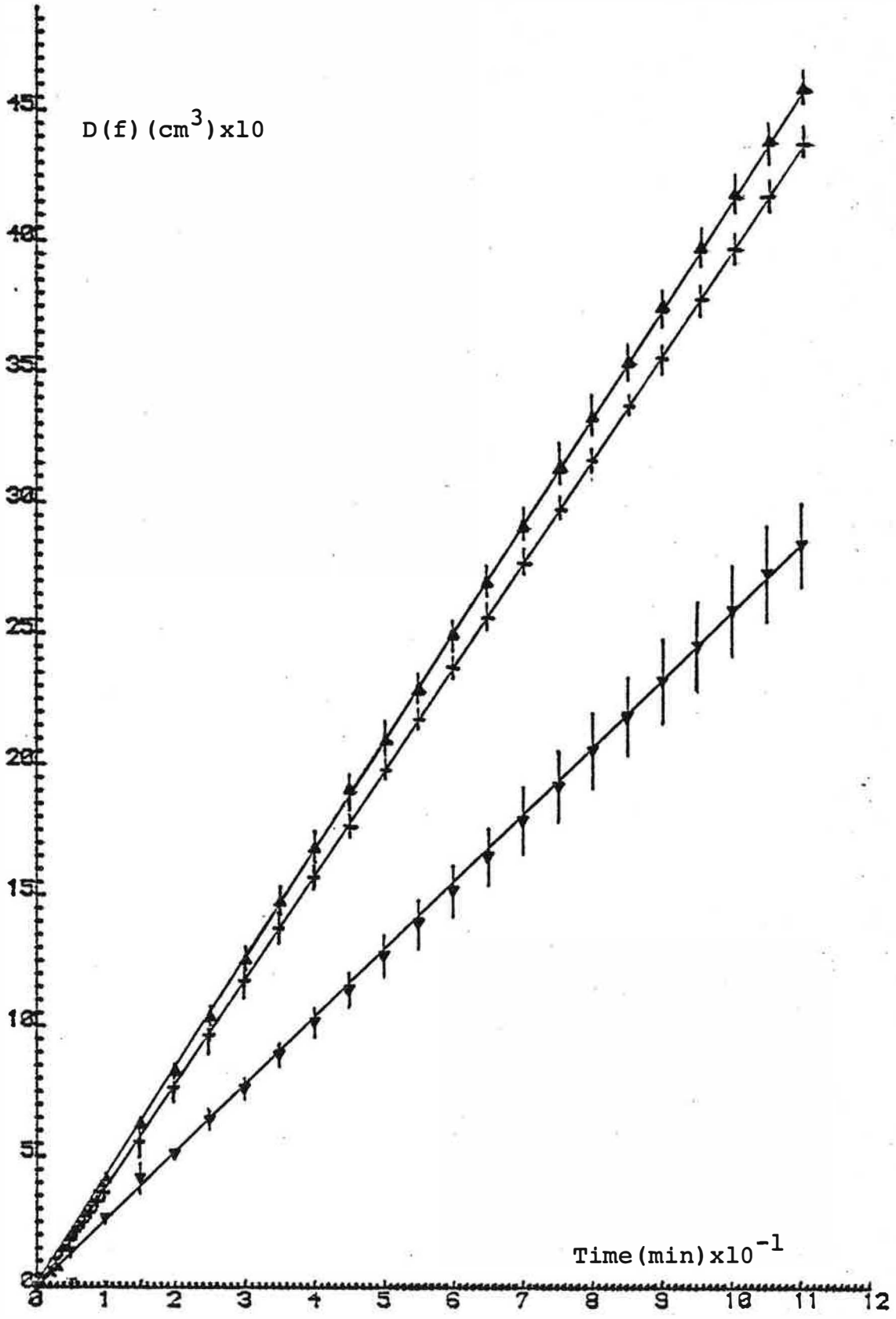


Figure 5.31. Paracetamol release from (▼) Miglyol, (+) Emulsion, (▲) aqueous solution.

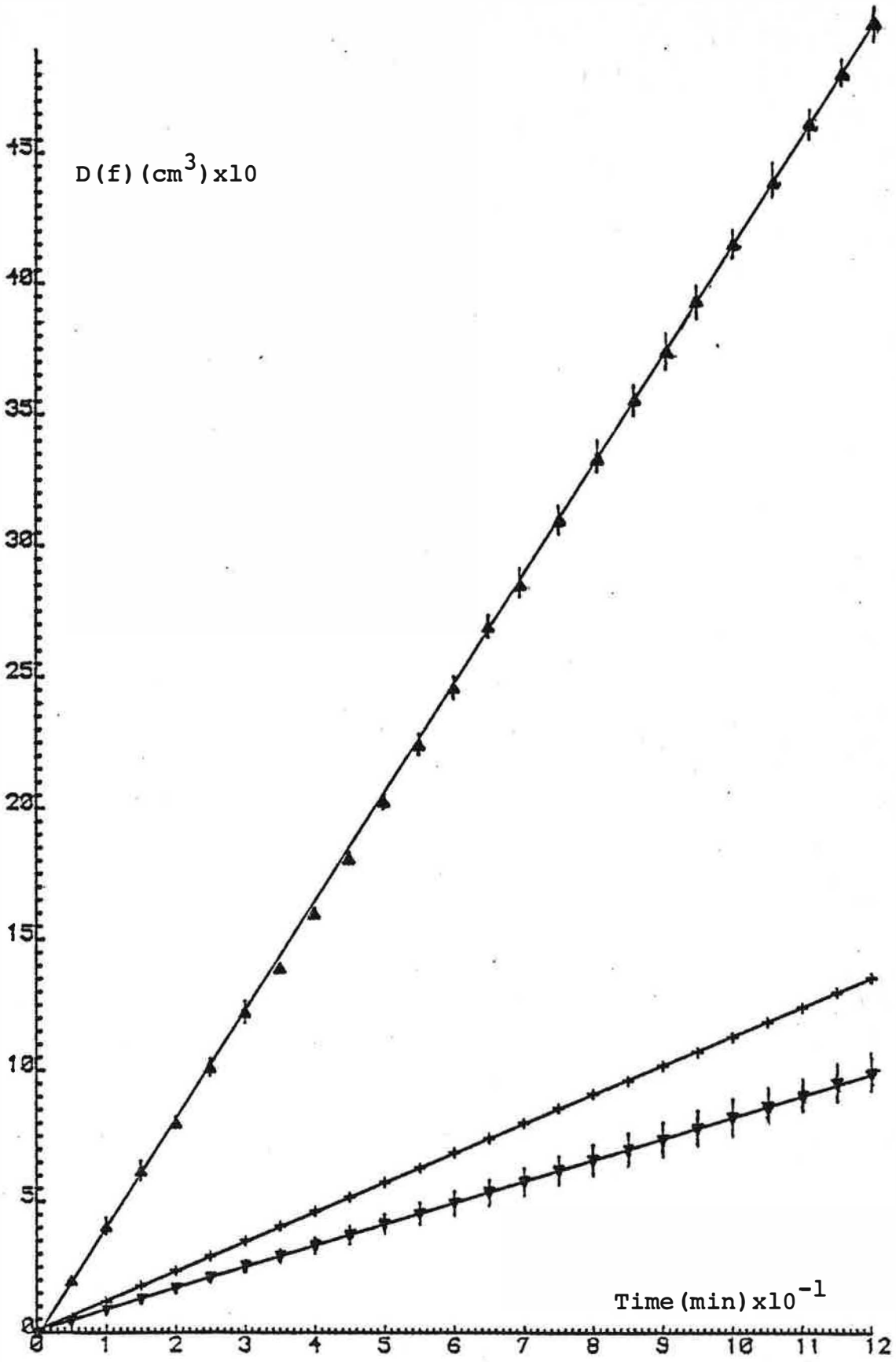


Figure 5.32. Phenacetin release from (▼) Miglyol, (+) Emulsion, (▲) aqueous solution.

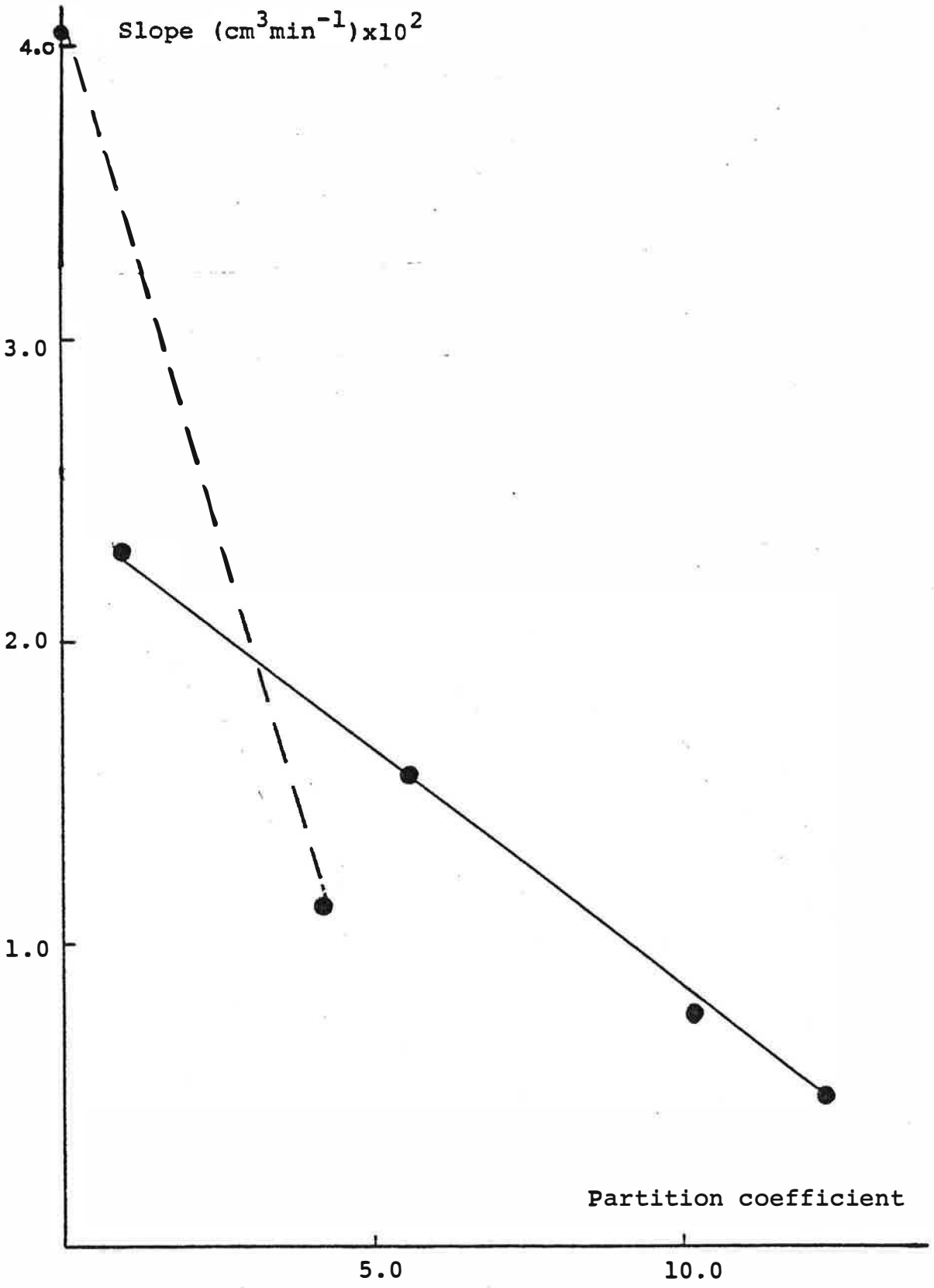


Figure 5.33. Relationship between the partition coefficient of the drug and the release from emulsion.

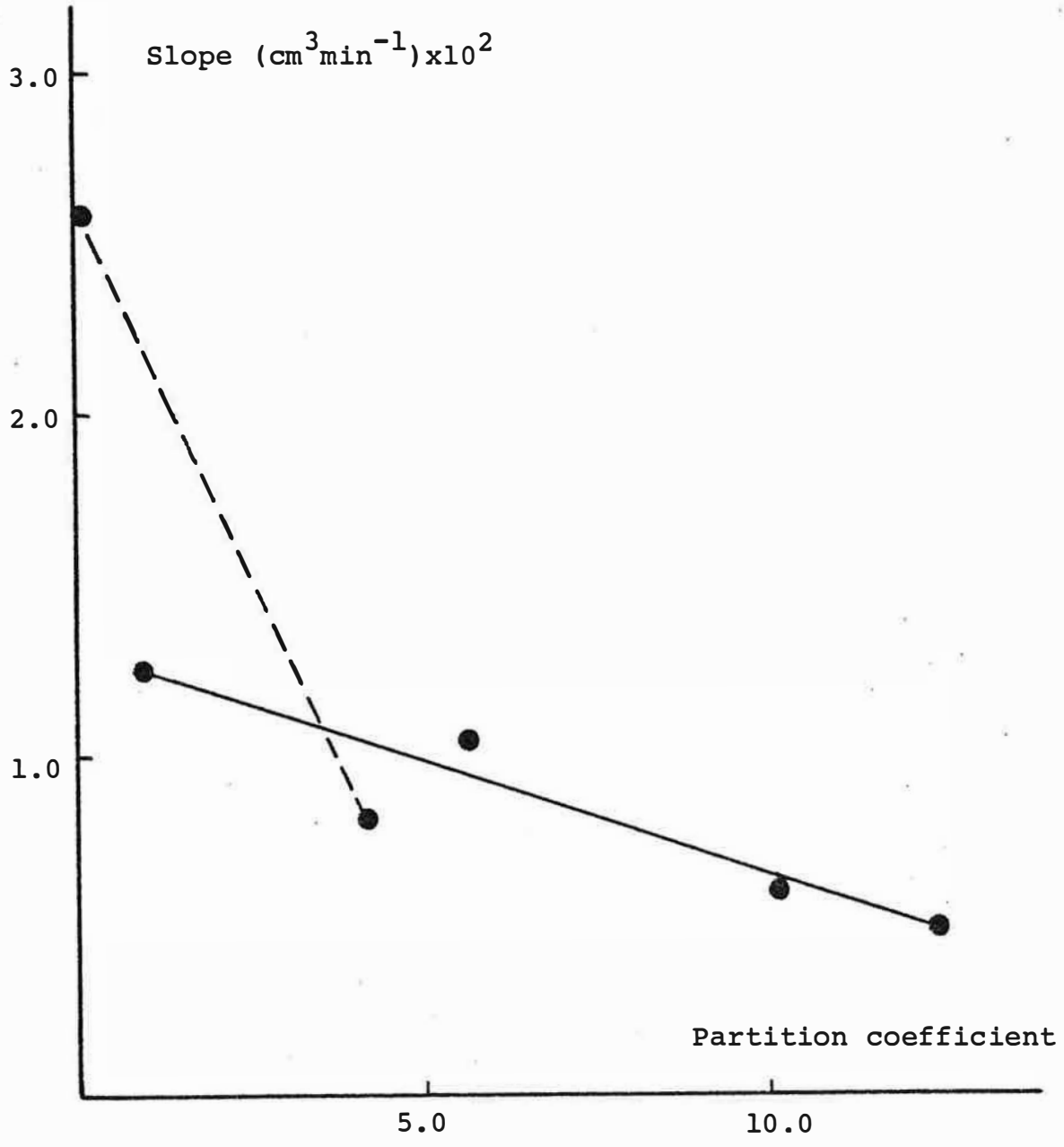


Figure 5.34. Relationship between the partition coefficient of the drugs and the release from the oily solution.

5.3.7 Effect of the oil viscosity on drug release from emulsions

In order to evaluate the effect of the oil viscosity on drug release, a study was made of the release of salicylic acid from emulsions prepared with Miglyol oil blends and Miglyol-812 gelled with a range of gelling agents.

First, blends of a more viscous and denser oil Miglyol 829 with Miglyol 812 were used to prepare the emulsions and release experiments were carried out from both the emulsions and the oil phases. Then, Miglyol 812 was thickened with different gelling agents such as Miglyol-Gel, Aerosil 200, Aerosil 300, and the drug release characteristics of these gels and the emulsions prepared with these gels were studied.

The oil/water phase volume ratio was kept constant at 50/50 and cetomacrogol at 1.0% w/v concentration was used to stabilize the emulsions. 0.1% w/v salicylic acid was added to the emulsions and the receptor solution was always distilled water.

5.3.7.1 Miglyol 812/Miglyol 829 mixtures

Miglyol 829 is a triglyceride mixture of saturated vegetable fatty acids of medium chain length (C_8-C_{10}) and succinic acid. This oil has a higher viscosity than Miglyol 812 and it has a density of 1.004 at 25°C.

In order to ensure that the nature of the oil did not change except for the viscosity, the partition coefficient experiments were carried out using the oil blends as the oil phases. There were no significant differences in

partition coefficient of salicylic acid which was 12.47±0.23, for every mixture.

The results of the salicylic acid release from the oil mixtures are shown in Figure 5.35 and the slopes of the lines and the viscosity of the oil mixtures are summarized in Table 5.30. All of the oil mixtures showed Newtonian flow (Figure 5.36). When the slopes of the release curves were plotted against the reciprocal of the viscosities of the oil mixtures, there was a linear relationship (Figure 5.37). Although drug release from the oil reduced with increasing viscosity, 6-fold increase in viscosity reduced the release rate by only 20%. Drug release from the emulsions prepared with these oils was not significantly different (Figure 5.38, Table 5.31). This can be attributed to the slow transport of the drug through the interfacial layer which was the rate-limiting step. Therefore the slow diffusion of the drug within the oil globule could not become significant and did not alter the release characteristics of the emulsions. As shown in Figure 5.39, the emulsions showed antithixotropic behaviour and the viscosities were not significantly different (Table 5.31).

5.3.7.2 Effect of "Miglyol-Gel" as a thickening agent on drug release from the oily solutions and the emulsions

Miglyol-Gel is produced by gelling Miglyol 812 neutral oil with an organically modified montmorillonite (Bentone) and is a cream-coloured substance with a pasty consistency.

The oil phases of the emulsions used for this portion of the study were prepared by mixing the Miglyol-Gel in

Table 5.30. Effect of the oil viscosity on drug release.

Miglyol 812/Miglyol 829 v/v ratio	η, 25°C (cP)	1/η, 25°C (cP^{-1})	Slope $cm^3\ min^{-1}$	Correlation coefficient	Degrees of freedom
100/0	23.46	0.0426	0.0052	0.9970	90
75/25	35.34	0.0283	0.0048	0.9987	67
50/50	54.85	0.0182	0.0044	0.9960	67
25/75	88.97	0.0112	0.0041	0.9953	67
0/100	146.57	0.0068	0.0039	0.9980	67

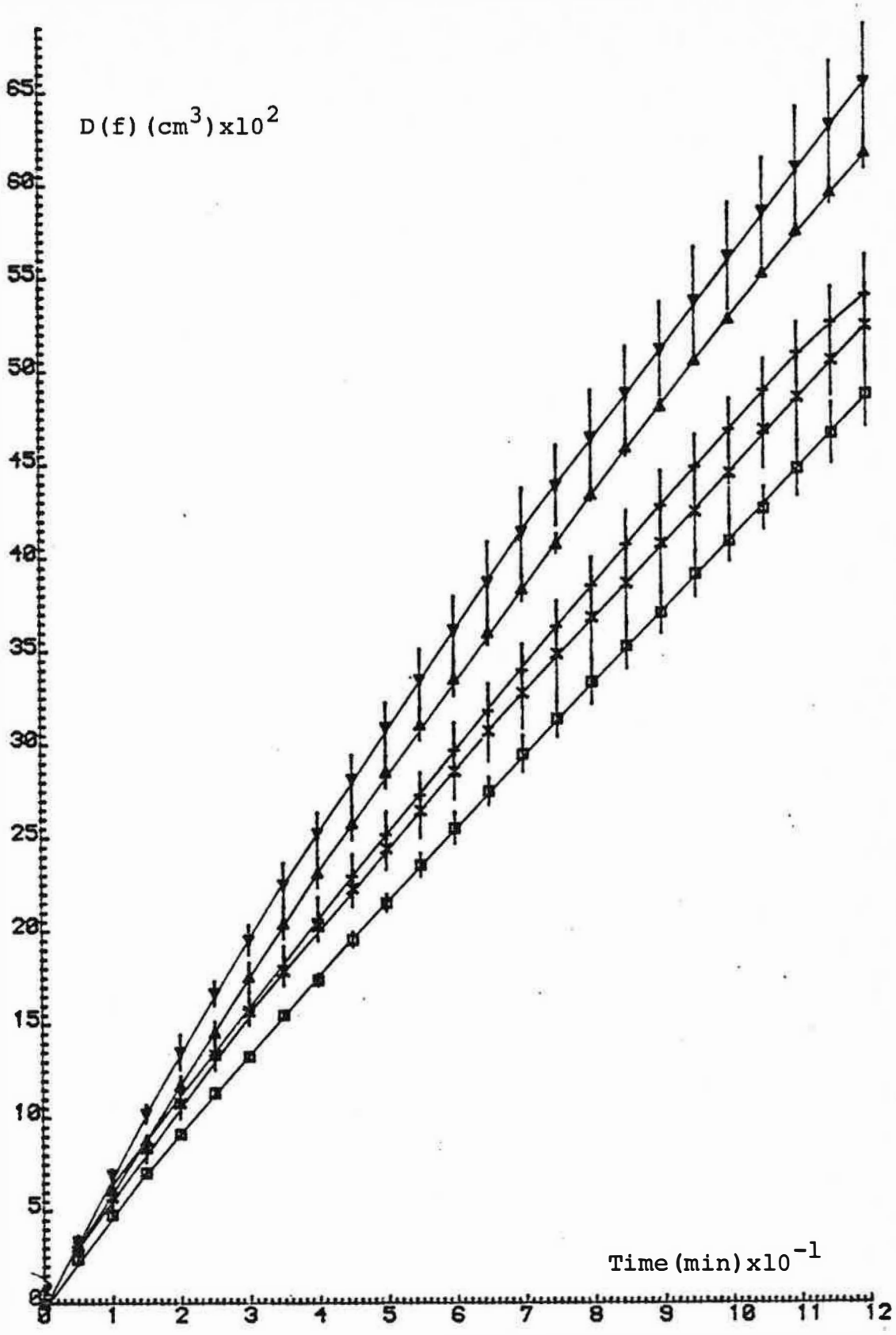


Figure 5.35. Salicylic acid release from oil blends. (▼) Miglyol 812, (▲) Miglyol 812/Miglyol 829 = 75:25, (+) Miglyol 812/Miglyol 829 = 50:50, (×) Miglyol 812/Miglyol 829 = 75:75, (□) Miglyol 829.

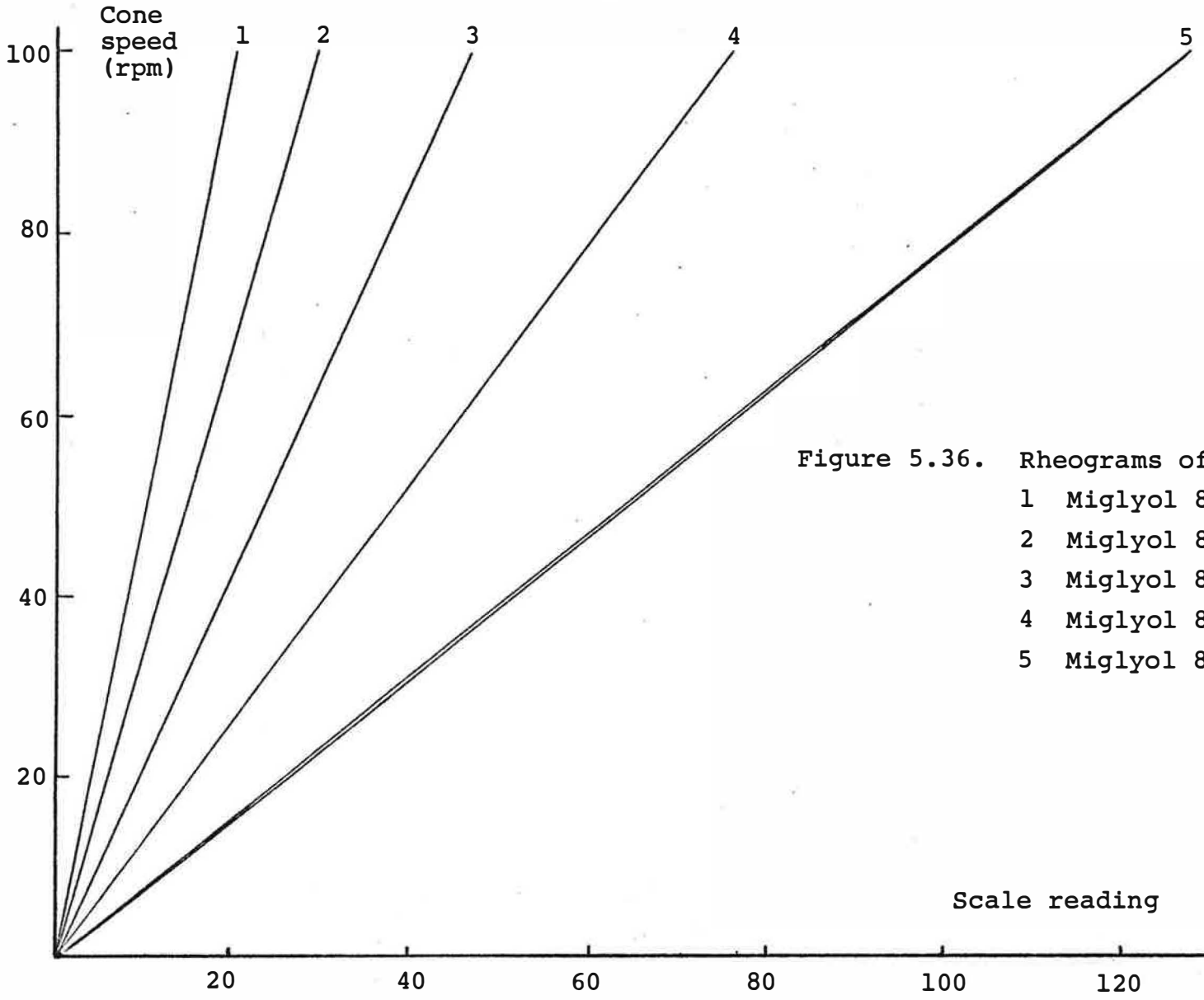


Figure 5.36. Rheograms of the oil mixtures at 25°C.

1 Miglyol 812.

2 Miglyol 812/Miglyol 829:75/25.

3 Miglyol 812/Miglyol 829:50/50.

4 Miglyol 8o2/Miglyol 829:25/75.

5 Miglyol 829.

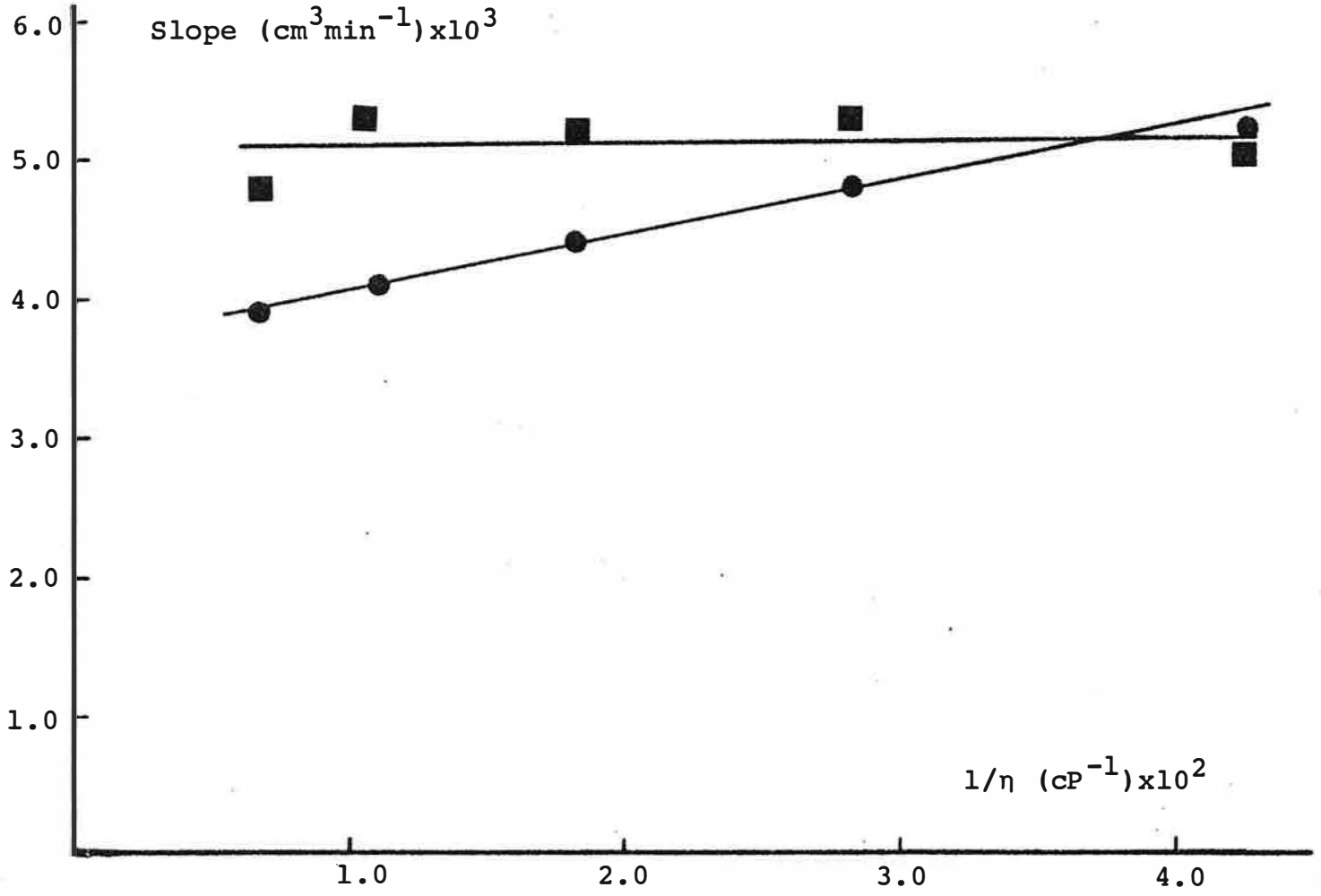


Figure 5.37. Effect of oil viscosity on salicylic acid release from (●) oil mixtures and (■) emulsions.

Table 5.31. Effect of the oil viscosity on drug release from emulsions.

Emulsion No.	Oil phase of the emulsion, Miglyol 812/Miglyol 829	Slope $cm^3\ min^{-1}$	Correlation coefficient	Degrees of freedom	η_{em} (cP) at 25°C	η_{oil} (cP) at 25°C
IV-1	100/0	0.0050	0.9989	90	10.45	23.46
IV-2	75/25	0.0053	0.9899	58	10.57	35.34
IV-3	50/50	0.0052	0.9997	67	10.45	54.85
IV-4	25/75	0.0053	0.9998	67	10.55	88.97
IV-5	0/100	0.0048	0.9978	90	11.12	146.57

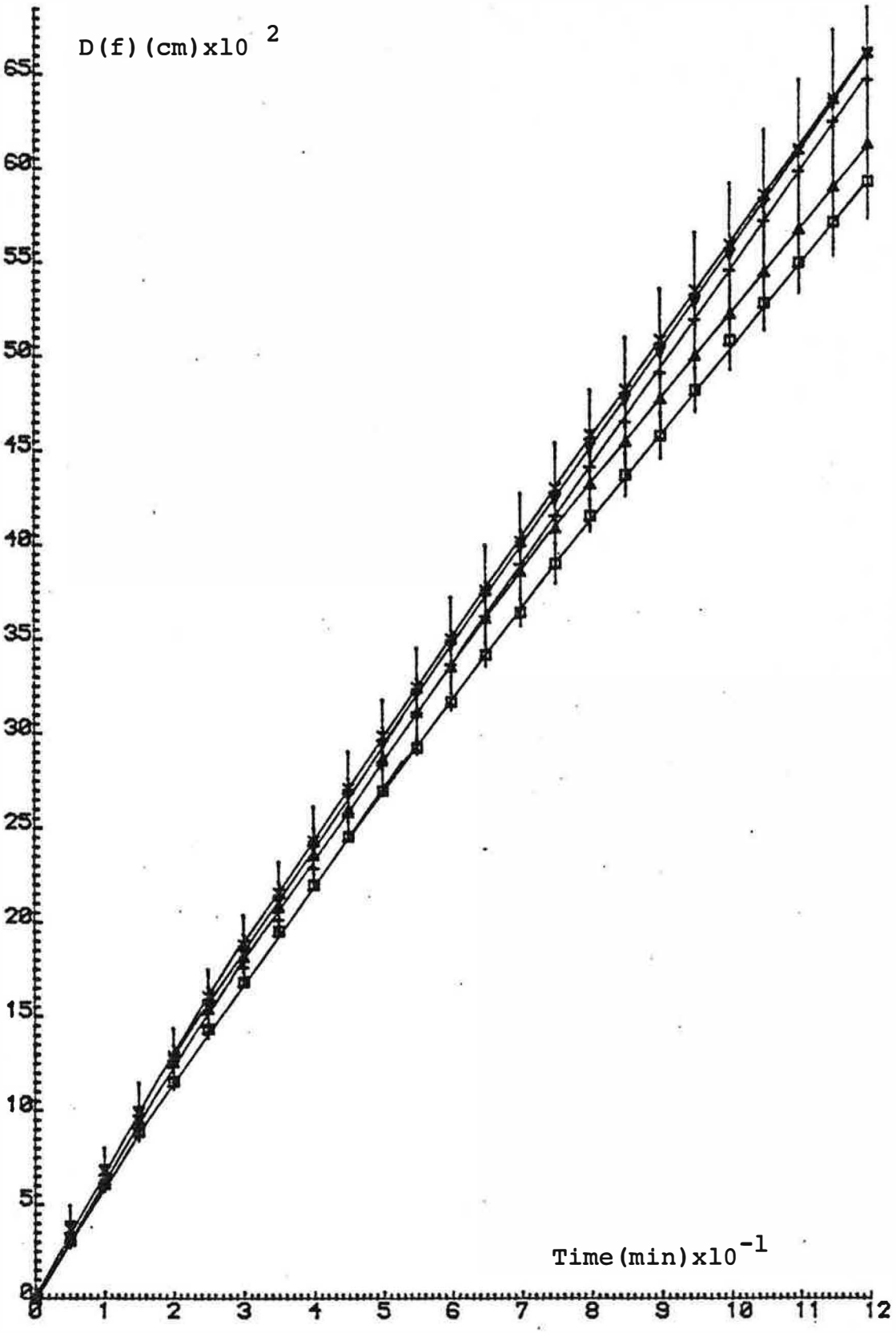


Figure 5.38. Salicylic acid release from the emulsions prepared with Miglyol 812, Miglyol 829 mixtures. (▲) Emulsion IV-1, (▼) Emulsion IV-2, (+) Emulsion IV-3, (×) Emulsion IV-4, (□) Emulsion IV-5.

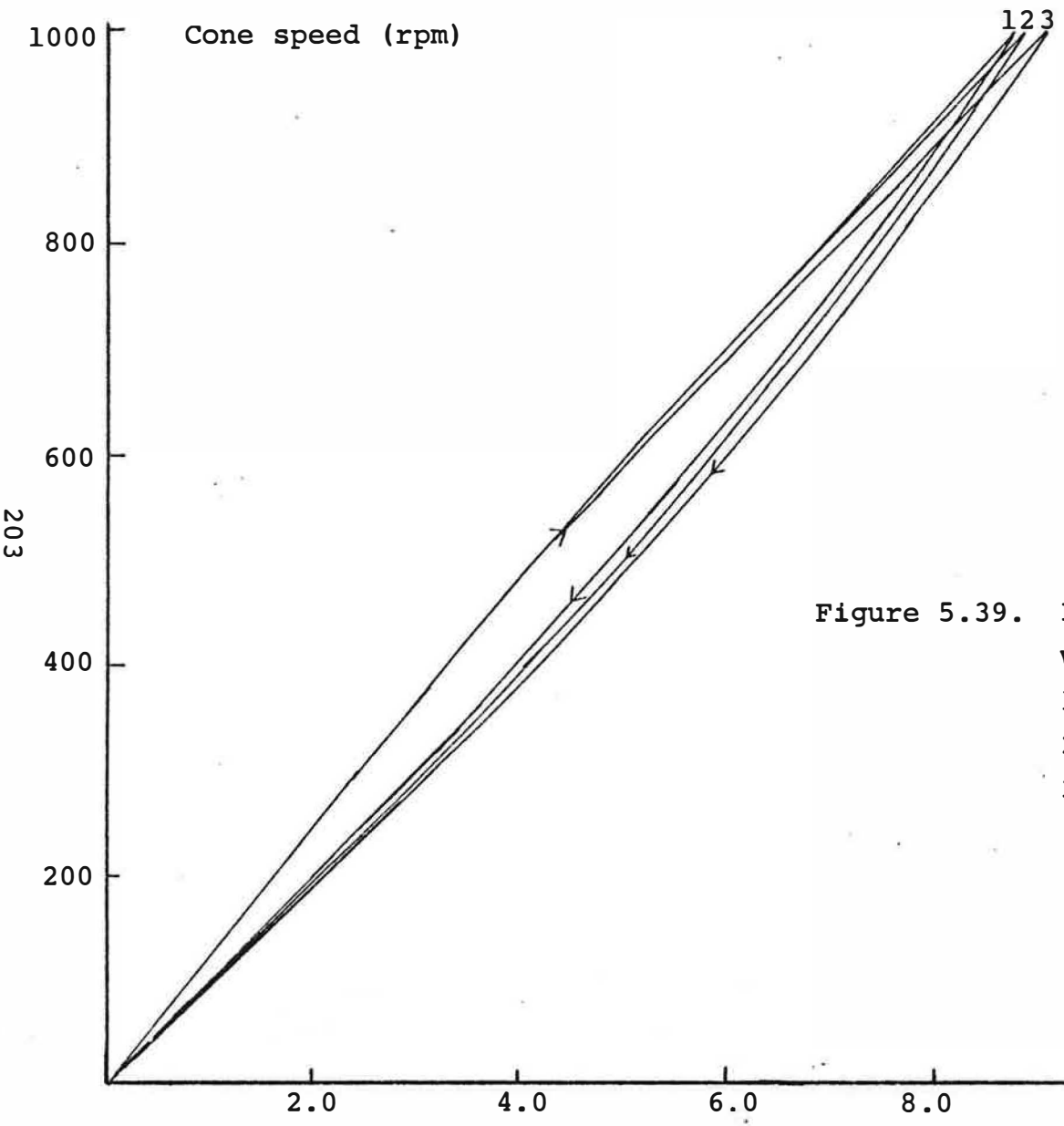


Figure 5.39. Rheograms of the emulsions prepared with oil mixtures at 25°C.
1 Emulsion IV-1 and IV-3.
2 Emulsion IV-2 and IV-4.
3 Emulsion IV-5.

Miglyol 812 and homogenizing the mixture by passing it through the hand homogenizer. Flow curves of these mixtures are shown in Figure 5.40 and the calculated viscosities are given in Table 5.32. Up to 5% w/v Miglyol-Gel concentrations, the gels showed Newtonian flow. On increasing concentration first pseudoplastic, then plastic flow were observed: at the highest concentrations thixotropic behaviour was superimposed (Figure 5.40). As can be seen from Figure 5.41 and Table 5.32, increasing Miglyol-Gel concentrations in the oil reduced the drug release. Figure 5.42 shows the relationship between the release and the viscosity of the oily gels.

The emulsions containing Miglyol-Gel in the oil phases also released the drug slower when the concentration of the Miglyol-Gel was increased. The release curves of these emulsions are shown in Figure 5.43, and the calculated slopes are given in Table 5.33. It is interesting to note that salicylic acid release from the standard emulsion which did not contain any gelling agent in the oil phase was somehow slower than these emulsions. This could be attributed to the change in the interfacial film such as a disruption of the film due to a competition between the Bentone molecules and cetomacrogol-1000. If this competition caused discontinuities or weak points in the film, salicylic acid molecules would leak and this would result in a faster drug release from the oil phase of the emulsion.

5.3.7.3. Effect of aerosils on drug release from the oil and emulsions

Aerosil is a silica produced from silicon tetrachloride

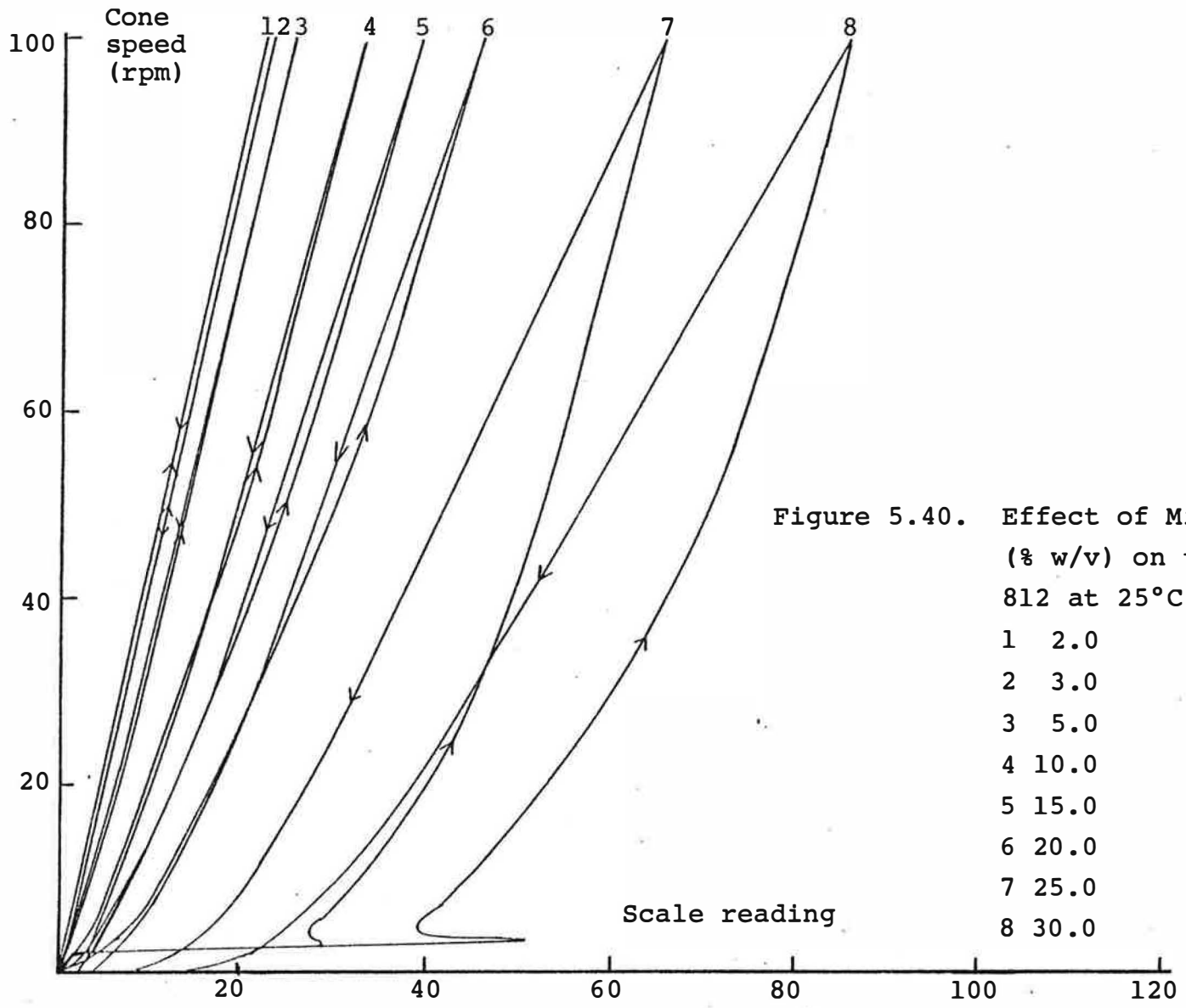


Figure 5.40. Effect of Miglyol-Gel concentration (% w/v) on the viscosity of Miglyol 812 at 25°C.

1 2.0
2 3.0
3 5.0
4 10.0
5 15.0
6 20.0
7 25.0
8 30.0

Table 5.32. Effect of viscosity on drug release from Miglyol. Gelling agent is Miglyol-Gel and salicylic concentration is 0.10% w/v.

% w/v Miglyol-Gel added	η (cP) at 25°C	$1/\eta$ cP^{-1}	Slope $cm^3\ min^{-1}$	Correlation coefficient	Degrees of freedom
2	26.82	0.0373	0.0049	0.9899	113
3	27.43	0.0365	0.0046	0.9980	9
5	36.57	0.0273	0.0043	0.9754	67
10	40.22	0.0248	0.0039	0.9862	67
15	47.53	0.0210	0.0033	0.9859	67
20	56.07	0.0178	0.0032	0.9760	113
25	82.89	0.0121	-	-	-
30	107.26	0.0093	-	-	-

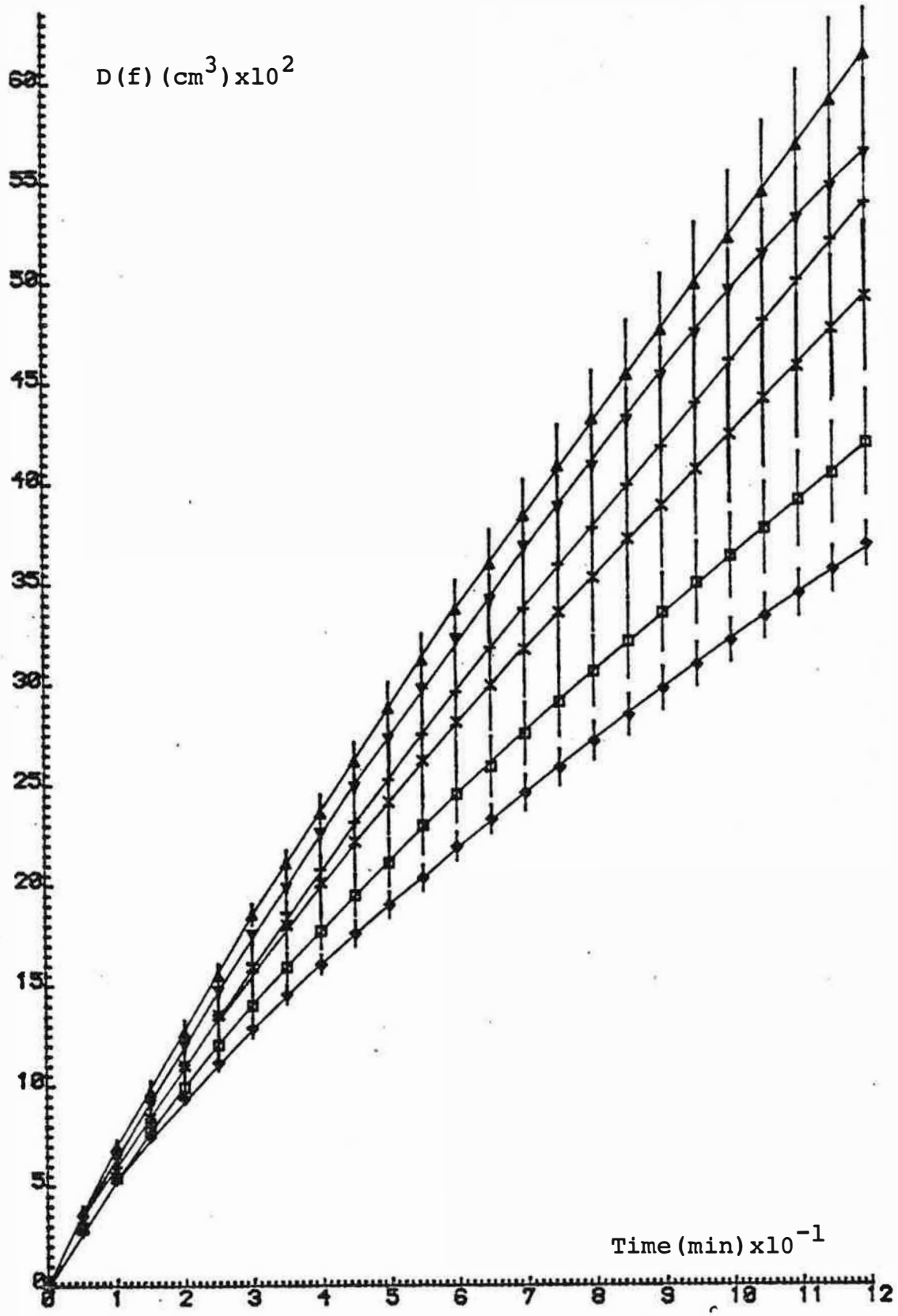


Figure 5.41. Effect of Miglyol-Gel concentration (% w/v) on drug release from oily solutions. (▲) 2.0, (▼) 3.0, (+) 5.0, (x) 10.0, (□) 15.0, (◆) 20.0.

Table 5.33. Effect of oil viscosity on drug release from Miglyol-Gel emulsions.

Emulsion No.	Concentration of MG % of the oil phase	Slope $cm^3\ min^{-1}$	Correlation coefficient	Degrees of freedom
V-1	4	0.0169	0.9941	67
V-2	5	0.0133	0.9909	90
V-3	6	0.0126	0.9881	62
V-4	10	0.0119	0.9958	90
Reference	0	0.0050	0.9989	90

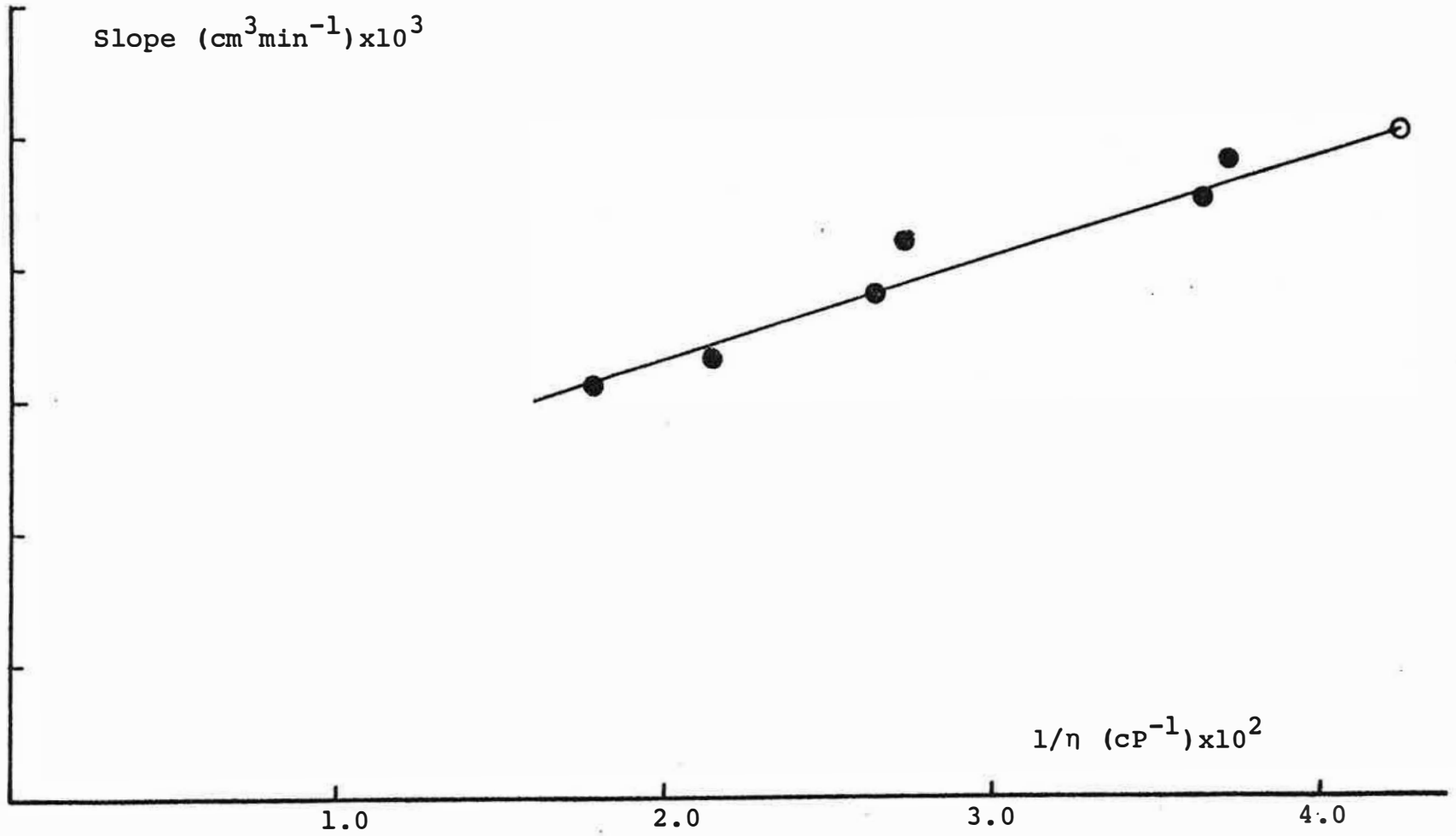


Figure 5.42. Effect of viscosity on drug release from (●) the oily gels prepared with Miglyol-Gel and (○) Miglyol 812 alone.

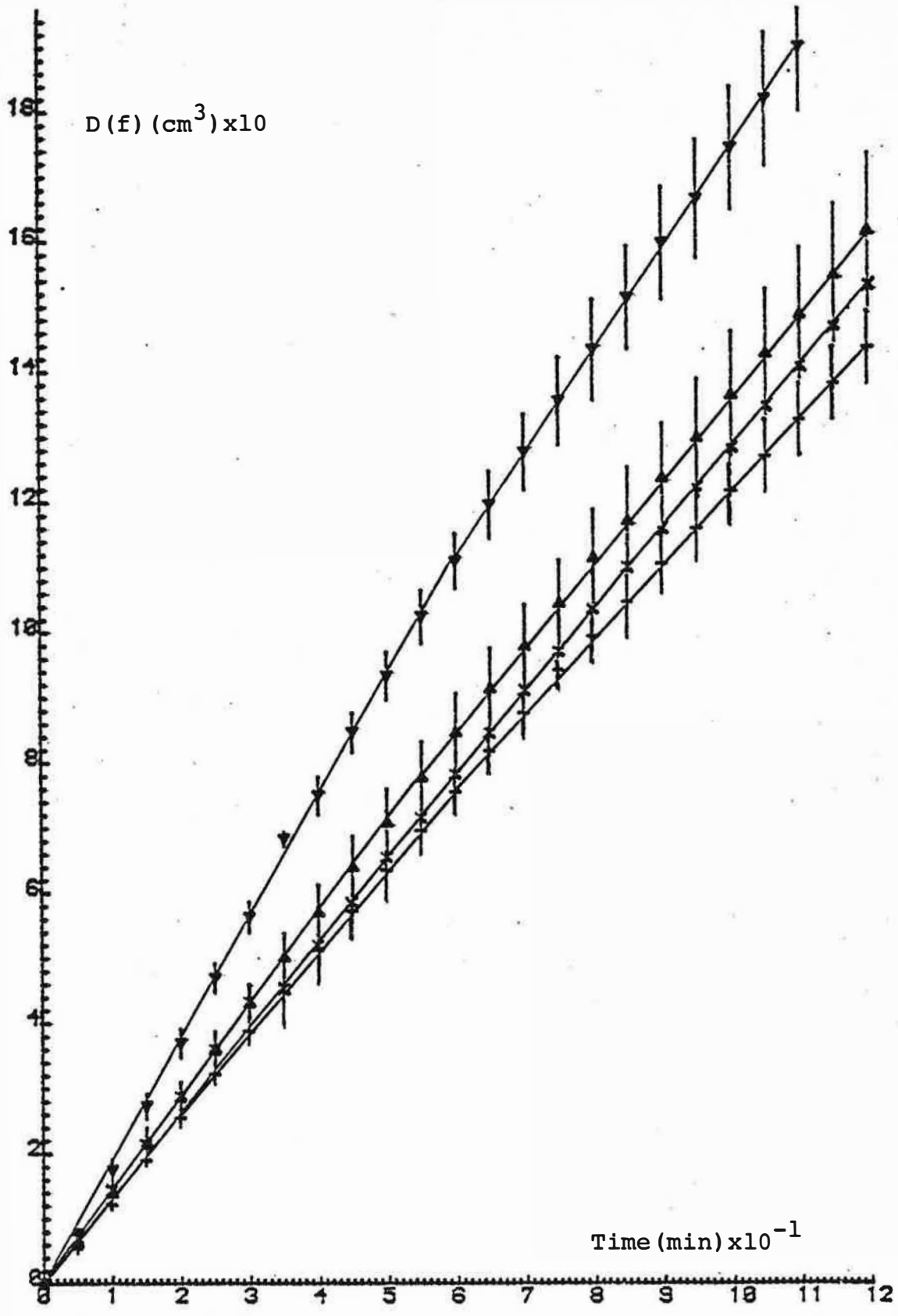


Figure 5.43. Effect of the concentration of Miglyol-Gel (% w/v) on salicylic acid release from emulsion. (▼) 4.0, (▲) 5.0, (×) 6.0, (+) 10.0.

by a flame hydrolysis process with oxygen-hydrogen gas, and is used widely in the pharmaceutical industry as a binder and glidant in tablets and as a suspending agent and viscosity modifier in suspensions, ointments and suppositories. Fumed silica forms gels when dispersed in organic liquids due to formation of a network structure of the silica particles by interparticle hydrogen bonding via the silanol groups on the silica surface (Young, 1958; Marshall and Rochester, 1975).

In order to evaluate the effect of oil viscosity on drug release from both oily solutions and emulsions, Aerosil 200 and Aerosil 300 were used as gelling agents.

First of all, the viscosity of the gels formed with these gelling agents was studied. As can be seen from Figures 5.44 and 5.45, the increasing concentrations of both gelling agents increased the viscosity of the gels formed. At low concentrations gels were Newtonian, but at higher concentrations thixotropy became more and more pronounced and the viscosity increased (Figures 5.44, 5.45 and 5.46). When drug release experiments were carried out, slower releases were observed than for oil alone in every case (Figures 5.47 and 5.48). The slopes of the release curves and the viscosity of the gels are summarized in Tables 5.34 and 5.35. However, although the viscosity of the gels reduced the release, the initial decrease in release with small increases in viscosity was more pronounced as shown in Figure 5.49, and further increases in viscosity did not seem to affect the release significantly. Also the experimental scatter reflects the difficulty in obtaining

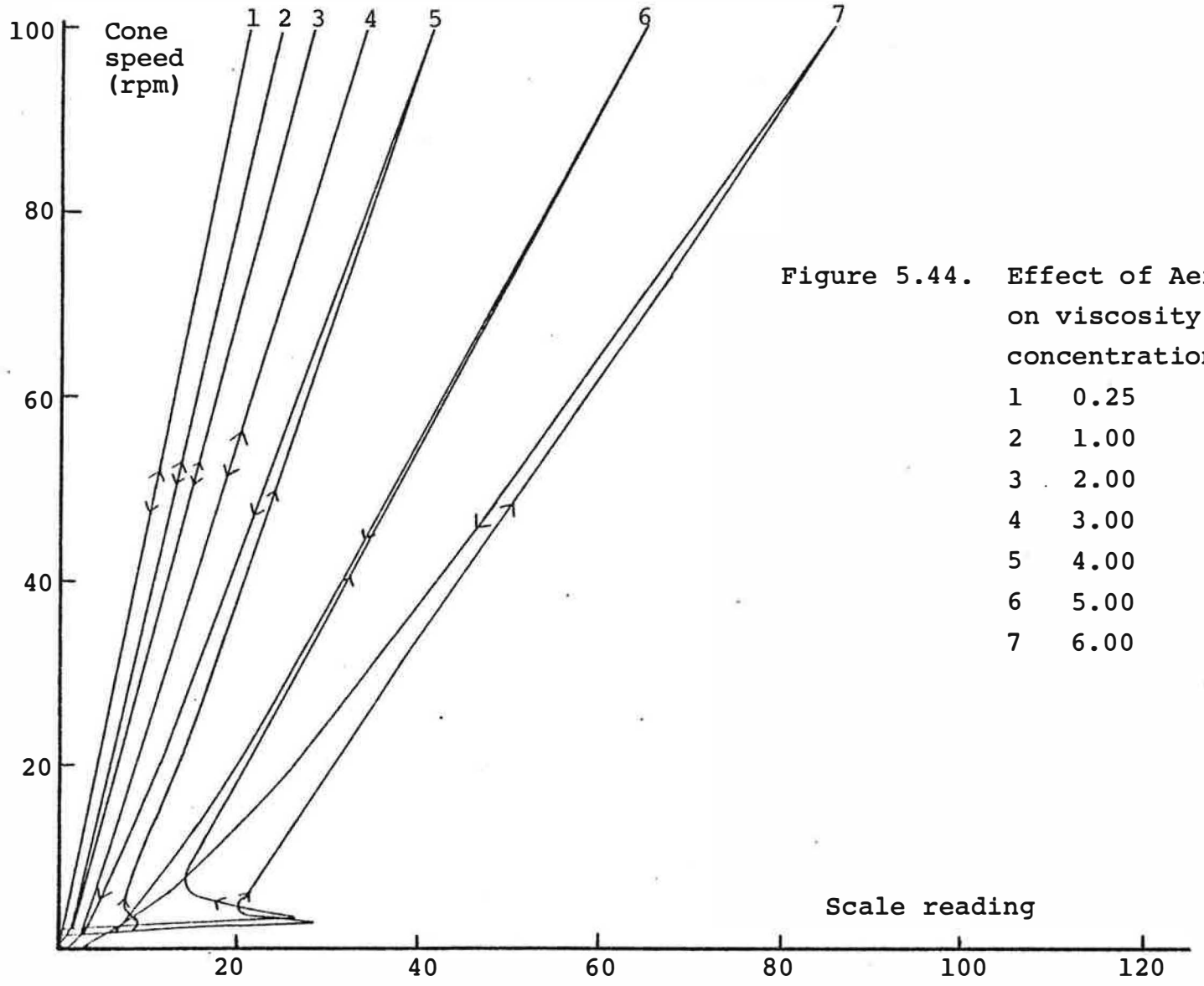


Figure 5.44. Effect of Aerosil-200 concentration on viscosity of oily gels. Aerosil-200 concentration (% w/v).

1 0.25
2 1.00
3 2.00
4 3.00
5 4.00
6 5.00
7 6.00

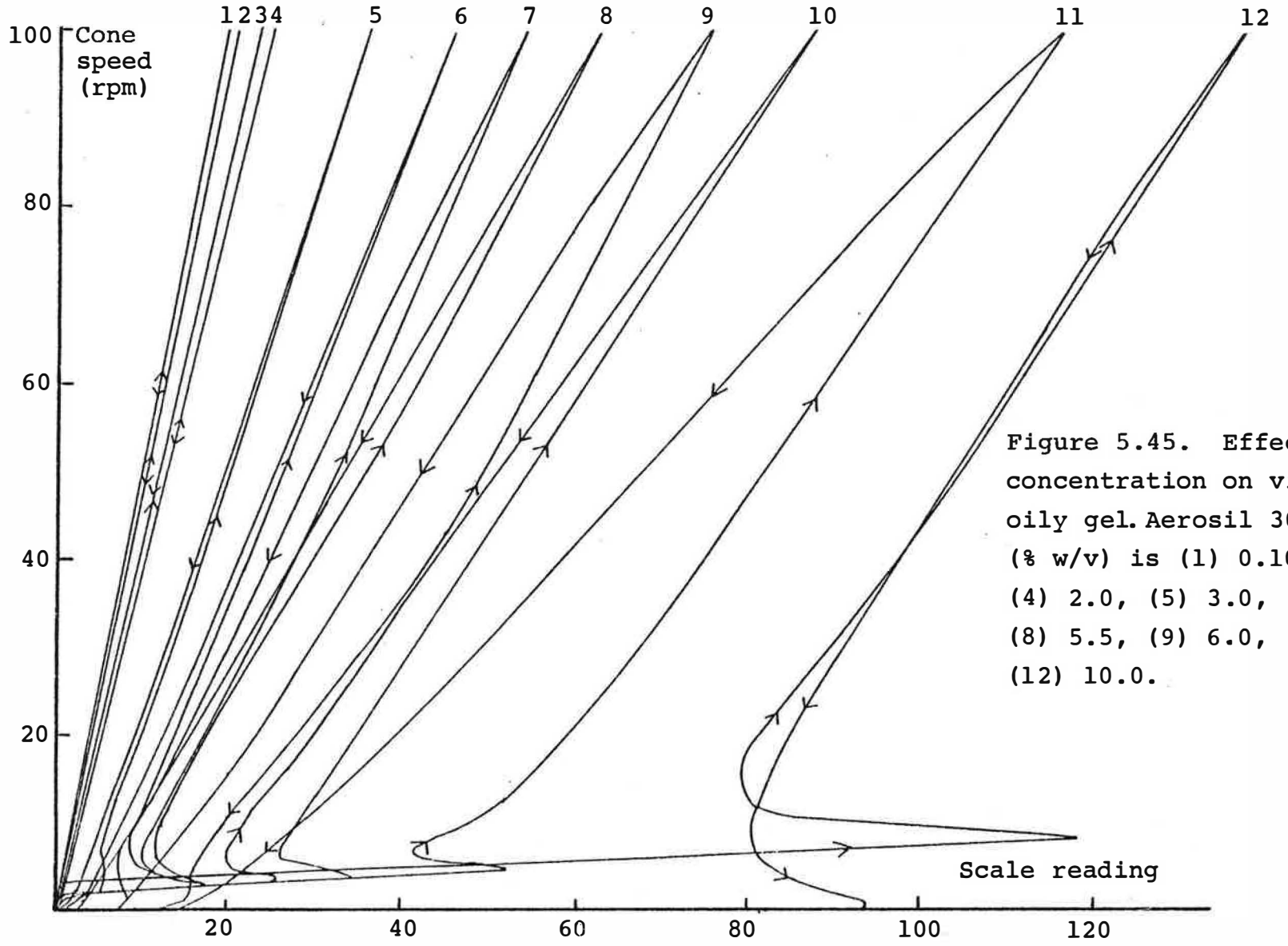


Figure 5.45. Effect of Aerosil-300 concentration on viscosity of the oily gel. Aerosil 300 concentration (% w/v) is (1) 0.10, (2) 0.25, (3) 1.0, (4) 2.0, (5) 3.0, (6) 4.0, (7) 5.0, (8) 5.5, (9) 6.0, (10) 7.0, (11) 8.0, (12) 10.0.

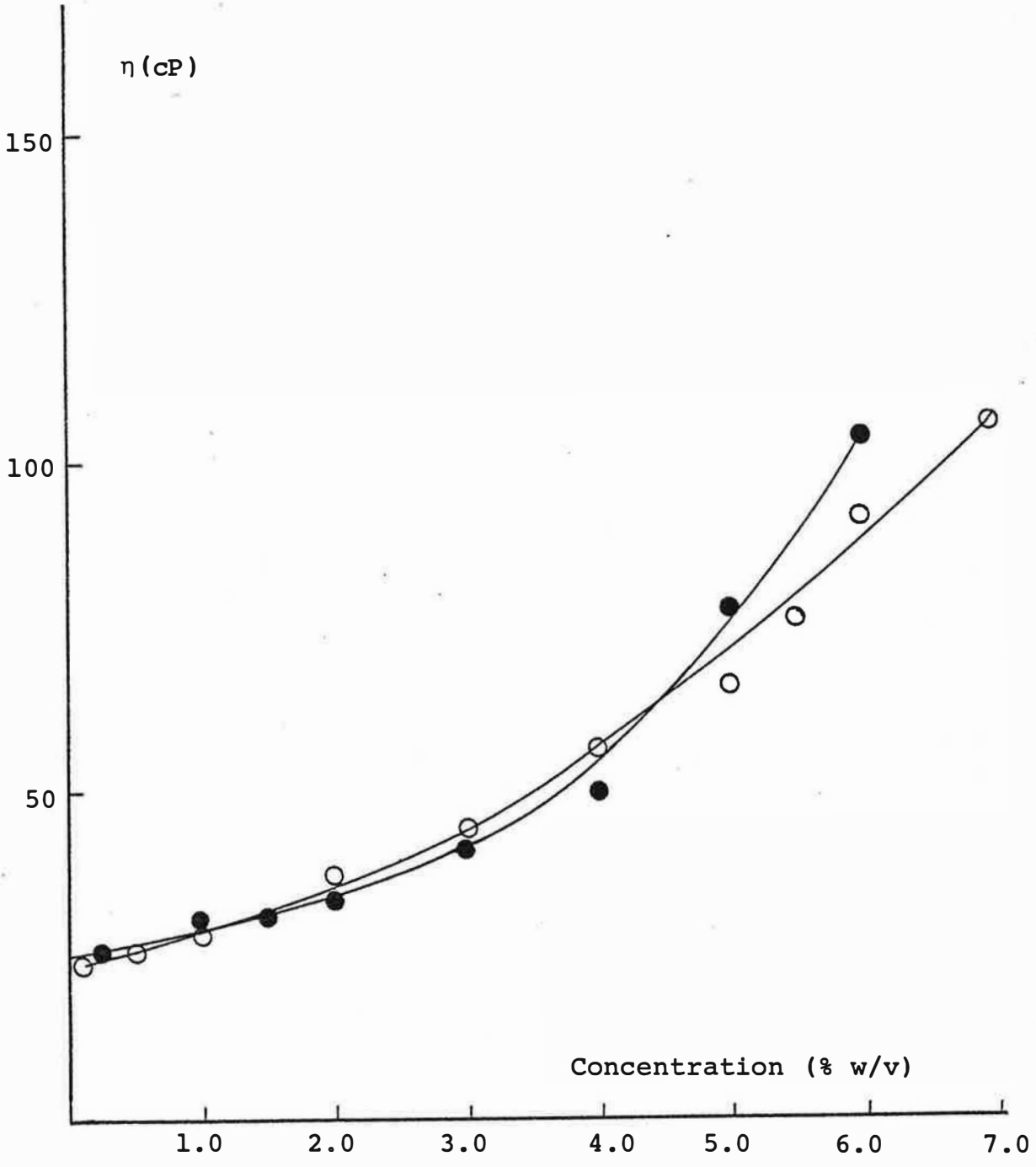


Figure 5.46. Effect of Aerosil concentration on viscosity of Miglyol gels. (●) Aerosil 200, (○) Aerosil 300.

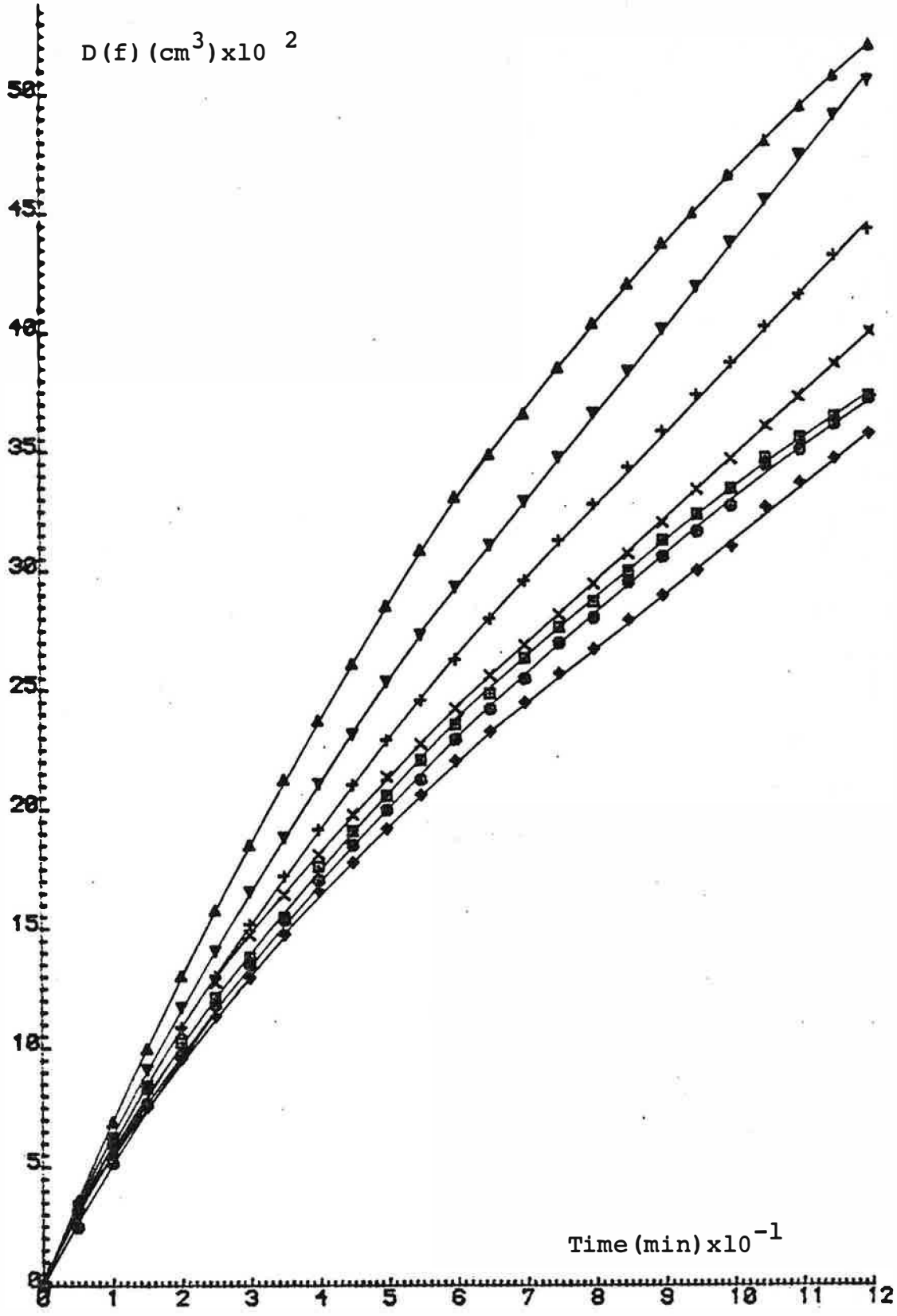


Figure 5.47. Effect of Aerosil-200 concentration on salicylic acid release from oily gels. Aerosil 200 concentration (% w/v); (▲) 0.1, (▼) 0.25, (+) 2.0, (×) 3.0, (□) 4.0, (○) 5.0, (◆) 6.0.

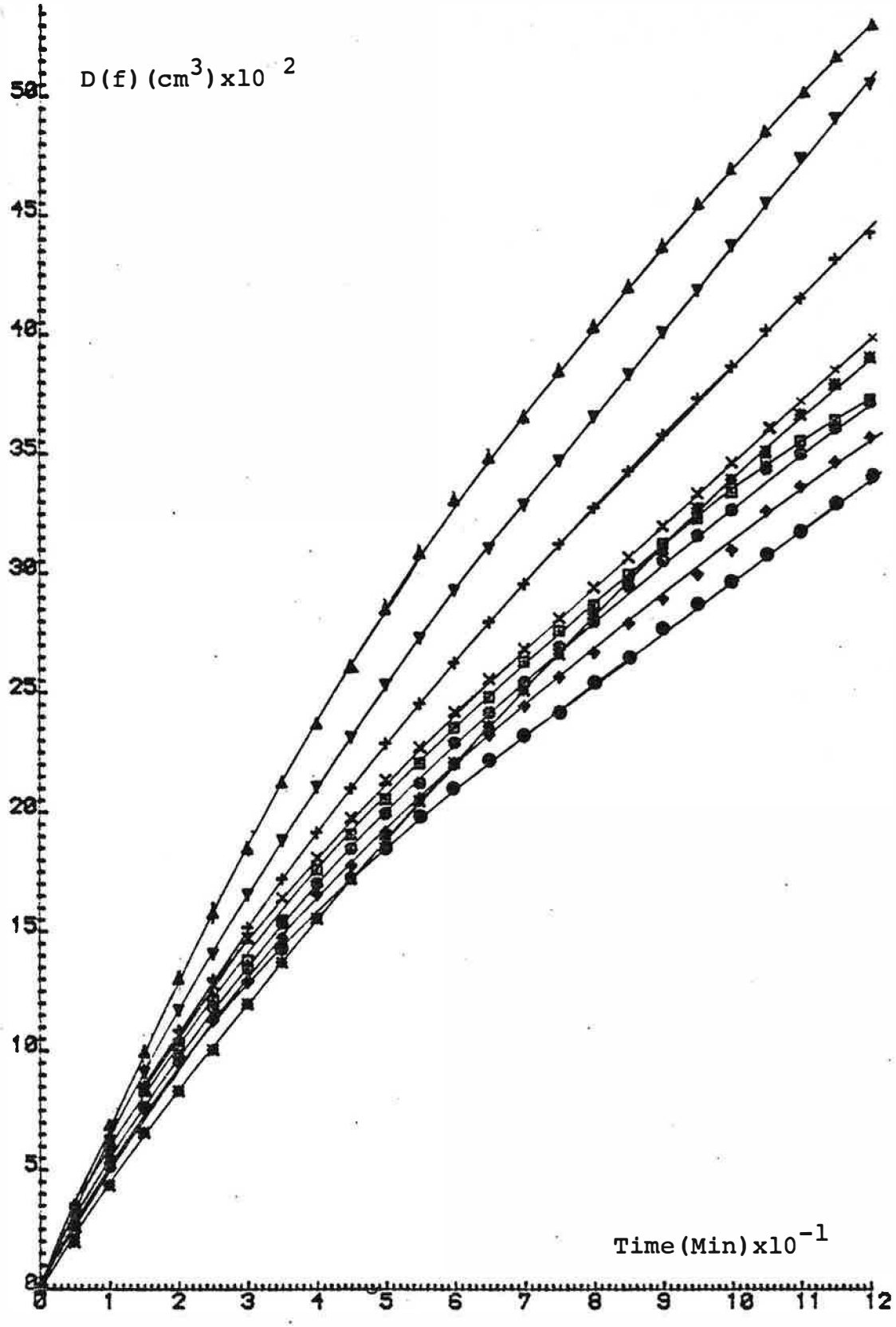


Figure 5.48. Effect of Aerosil 300 concentration on salicylic acid release from oily gels. Aerosil 300 concentration (% w/v) is (▲) 0.1, (▼) 0.25, (+) 0.5, (×) 2.0, (□) 3.0 and 5.0, (○) 6.0 and 7.0, (◆) 1.0, (✱) 1.5, (●) 4.0.

Table 5.34. Effect of oil viscosity on drug release from oily solutions. Gelling agent is Aerosil 200.

Concentration of A-200, % w/v of oil	Slope $cm^3\ min^{-1}$	Degrees of freedom	Correlation coefficient	η (cP) at 25°C	$1/\eta$ (cP^{-1})
0.10	0.0042	90	0.9955	23.77	0.042
0.25	0.0038	90	0.9940	25.59	0.039
2.00	0.0035	113	0.9674	33.83	0.030
3.00	0.0031	35	0.9949	40.83	0.025
4.00	0.0028	90	0.9935	49.98	0.020
5.00	0.0027	90	0.9955	78.62	0.013
6.00	0.0030	55	0.9952	104.22	0.010

Table 5.35. Effect of oil viscosity on drug release from oily solutions. Gelling agent is Aerosil 300.

Concentration of A-300, % w/v of oil	Slope $cm^3\ min^{-1}$	Degrees of freedom	Correlation coefficient	η (cP) at 25°C	$1/\eta$ (cP^{-1})
0.10	0.0042	74	0.9943	23.77	0.048
0.25	0.0038	113	0.9892	25.29	0.039
0.50	0.0035	74	0.9920	25.29	0.039
1.00	0.0029	90	0.9933	28.34	0.035
1.50	0.0032	90	0.9920	30.47	0.033
2.00	0.0031	74	0.9933	37.18	0.027
3.00	0.0028	74	0.9909	44.00	0.023
4.00	0.0024	74	0.9857	56.07	0.018
5.00	0.0028	67	0.9903	66.13	0.015
6.00	0.0027	90	0.9861	92.03	0.011
7.00	0.0027	90	0.9948	106.65	0.009
0	0.0052	90	0.9970	23.77	0.042
8.00	-	-	-	141.39	0.007
10.00	-	-	-	334.58	0.003

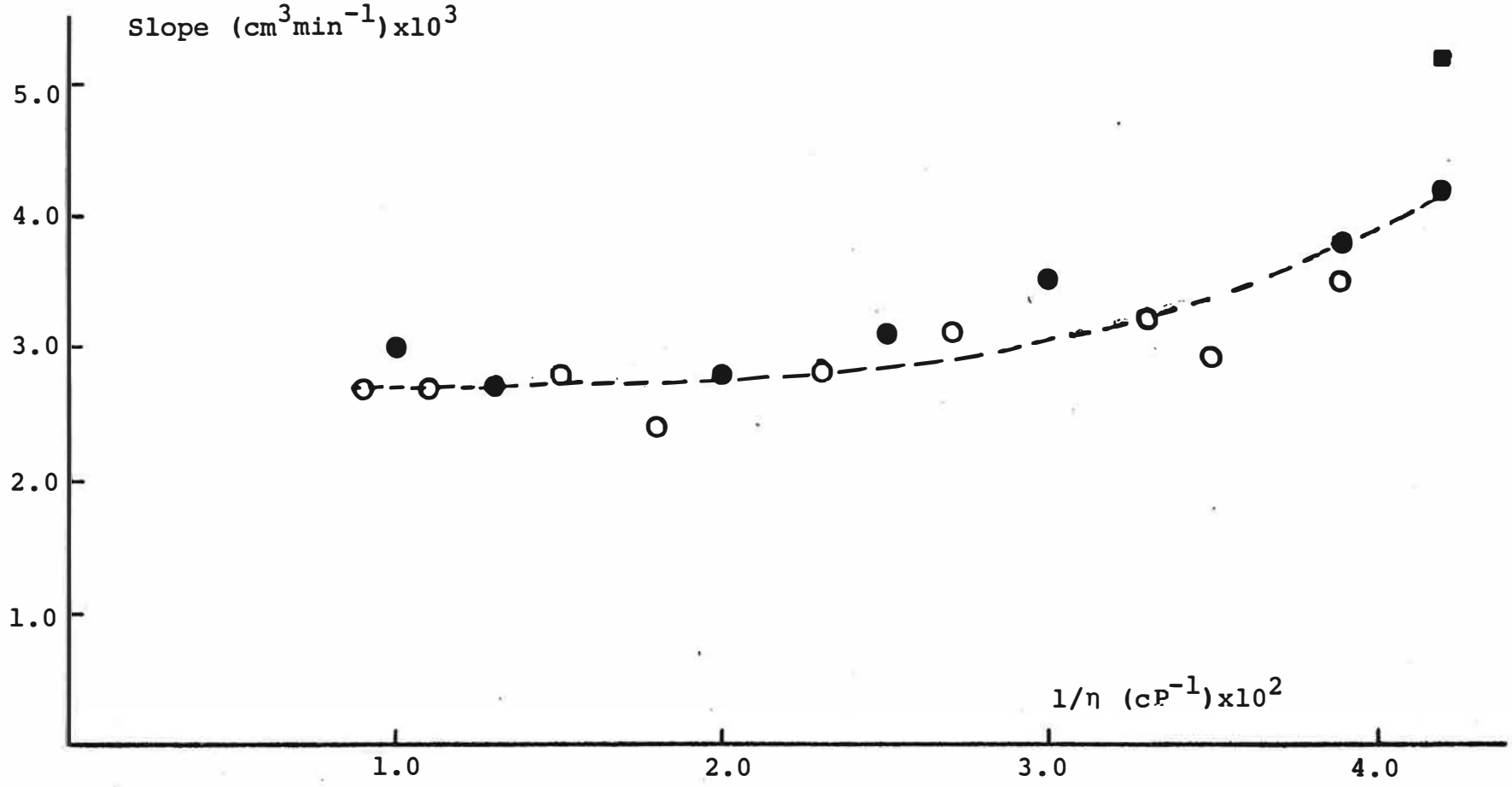


Figure 5.49. Effect of viscosity on salicylic acid release from Miglyol (■) and gels produced with Aerosil 200 (●), Aerosil 300 (○).

reproducible data in this particular experiment. In order to evaluate the possibility of salicylic acid interacting with silanol groups, partition coefficient experiments were carried out in the presence of Aerosil 200 and Aerosil 300 at varying concentrations. There was no significant difference and the mean partition coefficient of 12.79 was calculated with a standard deviation of ±0.38 for 17 samples. However, during the experiments gelling agents leaked out of the oil phase and sedimented at the bottom of the aqueous layer. This might suggest a possibility of the blockage of the membrane pores by the particles resulting in slower release of salicylic acid. The unexpectedly slow releases observed, especially at very low concentrations of gelling agents, could simply be due to the blocked pores in the membrane. According to the manufacturers' data, the average primary particle size is 12 nanometers and 7 nanometers for Aerosil 200 and Aerosil 300 respectively and these are well above the average pore diameter of Visking tubing which is 24°A. Therefore Aerosil particles cannot possibly block the membrane pores. Also, salicylic acid release from the aqueous solution containing up to 1% w/v Aerosil was not significantly different than release from aqueous solution. Release experiments were not performed for more than 1% w/v Aerosil concentrations, because there was a rapid sedimentation of silica particles from the aqueous solution. Another possible cause for the slow release rates from these gels could be the entrapment of salicylic acid molecules in the network formed by the silicon dioxide molecules by interparticle hydrogen bonding. If this network formation

acts like a matrix, release of salicylic acid from these gels could be matrix-controlled rather than simple diffusion controlled. When there is enough silicon dioxide to form such a network, release could be retarded and further addition of silicon dioxide might not further change the release pattern of these gels although this will increase the viscosity of the gels. However, the results did not prove this adequately and further work may show that these gels have potential as sustained release systems even when low concentrations of the gelling agentsare present.

The irreproducible results were mainly due to the difficulty in maintaining the properties of the gels during the experiment. It has been reported that the gel properties were critically dependent on the preparative method (Sherriff and Enever, 1979). Slightly different consistencies were observed when replicate gels were prepared using the same method. Similarly, during the introduction of the samples into the donor cell or during the experiment, the network structure could be destroyed or at least disturbed which in turn caused the experimental scatter. Emulsions containing varying concentrations of Aerosil 200 and Aerosil 300 in their oil phases were prepared with 1% w/v cetomacrogol. The oil/water ratio was again 50/50 and salicylic acid concentration was 0.10% w/v. Increasing Aerosil concentrations increased the viscosity of the emulsions and those containing about 5% w/v and more Aerosil in the oil phase were not liquid but had a cream-like consistency. This was due to the presence of Aerosil particles in the aqueous phases as well as the oil phases of the emulsions. As mentioned

earlier, leaking of Aerosil particles from the oil phase, which was clearly observed during the partition coefficient experiments, would thicken the aqueous phase of the emulsion resulting in semi-solid emulsions.

Figures 5.50 and 5.51 show the releases from the emulsions containing Aerosil 200 and Aerosil 300 in the oil phases at varying concentrations. The calculated slopes of the curves are summarized in Tables 5.36 A and 5.36B, together with the expected viscosities of the oil phases. As shown in Figure 5.52, the experimental results suggest that the effect of the oil viscosity on salicylic acid release from emulsions was not significant, and there was experimental scatter and difficulty in obtaining reproducible data. Although the range of the oil viscosities studied was very wide (Table 5.36), the release characteristics of the emulsions were similar. This could again be attributed to the interfacial barrier. The addition of silicon dioxide particles can contribute to the structure of the interfacial film forming almost a solid barrier and which can affect the transport of salicylic acid from oil to the aqueous phase of the emulsion. Once this solid coating is formed around the oil globules, it will produce a rate-limiting factor and further increase in the oil viscosity cannot influence the release any further. Therefore, release from the emulsions would not be significantly different.

In conclusion, although there was an indication that increasing the viscosity of the oil affected the drug release from emulsion, the results did not prove this adequately. The experimental method might be responsible for the

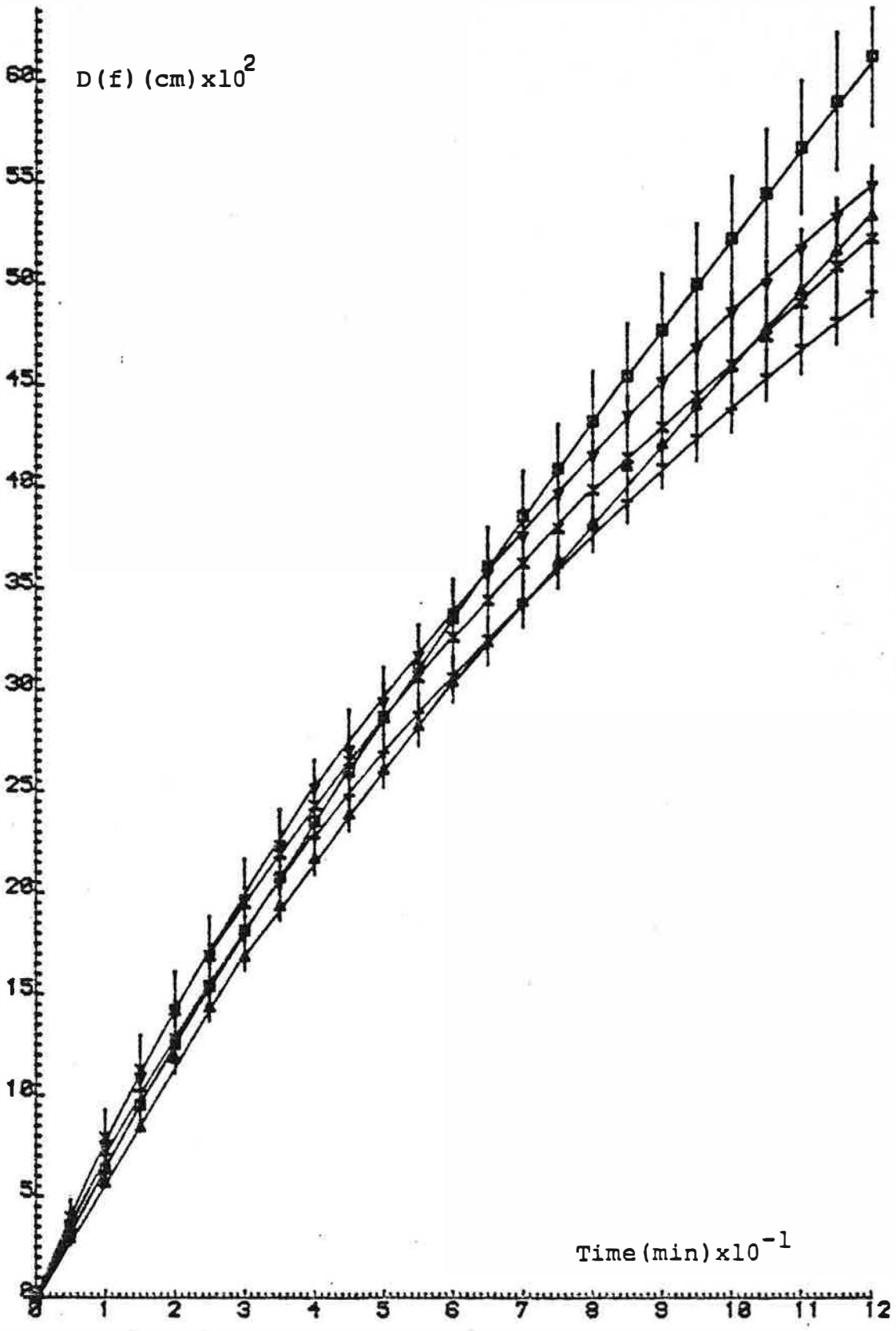


Figure 5.50. Salicylic acid release from emulsions containing Aerosil 200. (▼) Emulsion VI-1, (▲) Emulsion VI-2, (×) Emulsion VI-3, (+) Emulsion VI-4, (□) Miglyol emulsion with no gelling agent.

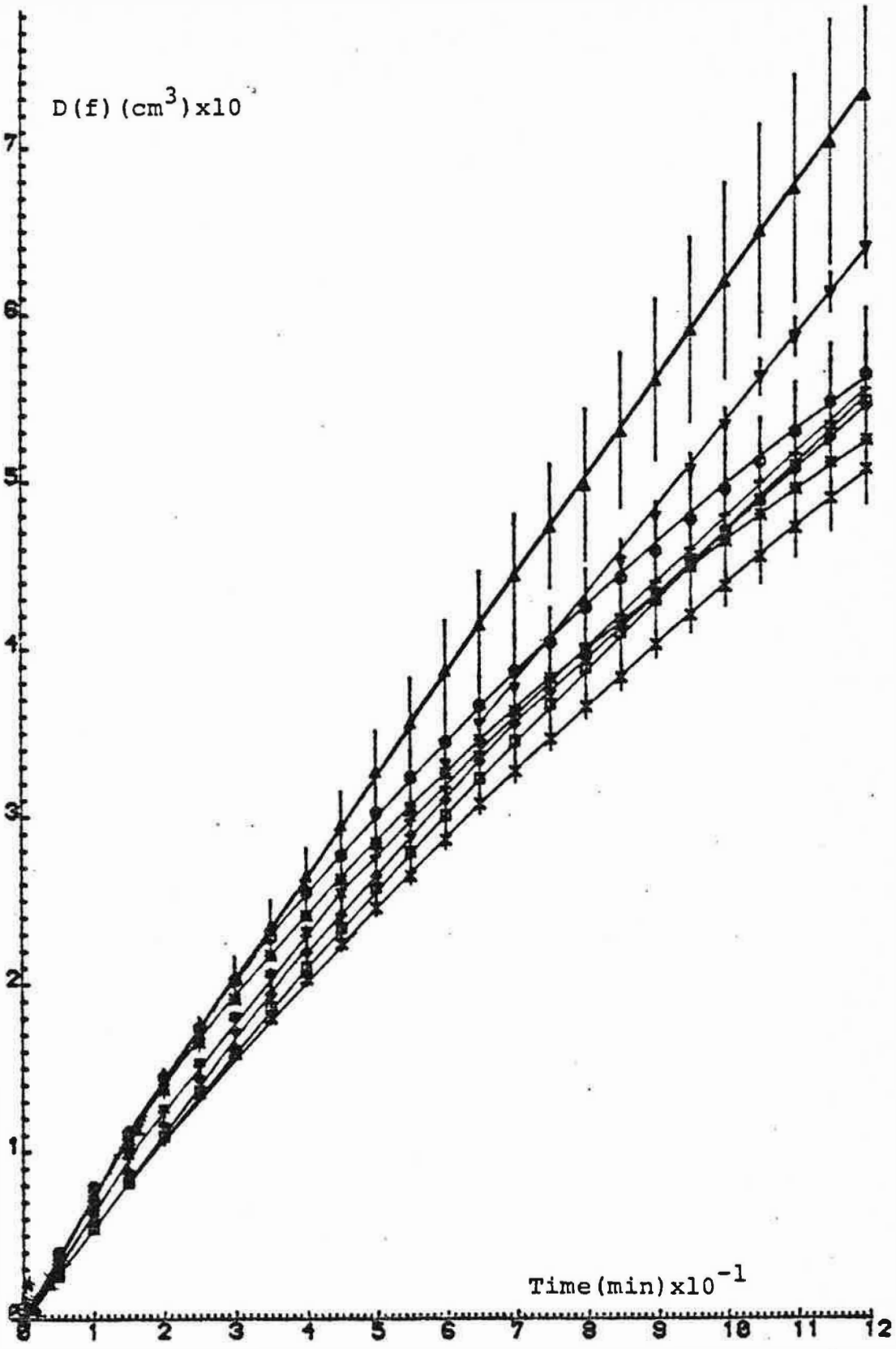


Figure 5.51. Salicylic acid release from emulsions containing Aerosil 300. (▼) Emulsion VII-1, (▲) Emulsion VII-2, (○) Emulsion VII-3 and VII-5, (+) Emulsion VII-6, (□) Emulsion VII-7, (◆) Emulsion VII-4, (✱) Emulsion VII-8, (×) Emulsion VII-9.

Table 5.36. Effect of the oil viscosity on drug release from emulsion.

A. Aerosil 200

Emulsion No.	Conc. of the gelling agent in the oil % w/v,	η_{oil} (cP), 25°C	$1/\eta_{oil}$ (cP^{-1})	Slope $cm^3\ min^{-1}$	Correlation coefficient	Degrees of freedom
VI-1	2.0	33.83	0.030	0.0041	0.9937	90
VI-2	5.0	78.62	0.013	0.0041	0.9931	90
VI-3	6.0	104.22	0.010	0.0040	0.9911	90
VI-4	8.0	546.07	0.002	0.0039	0.9815	90
B. Aerosil 300						
VII-1	0.5	25.29	0.039	0.0056	0.9933	67
VII-2	1.0	28.34	0.035	0.0051	0.9993	44
VII-3	1.5	30.47	0.033	0.0044	0.9963	90
VII-4	2.0	37.18	0.027	0.0041	0.9972	44
VII-5	2.5	39.22	0.025	0.0044	0.9943	90
VII-6	3.0	44.00	0.023	0.0043	0.9827	67
VII-7	4.0	56.07	0.018	0.0042	0.9843	67
VII-8	5.5	74.50	0.013	0.0039	0.9939	90
VII-9	7.0	106.65	0.009	0.0037	0.9915	90

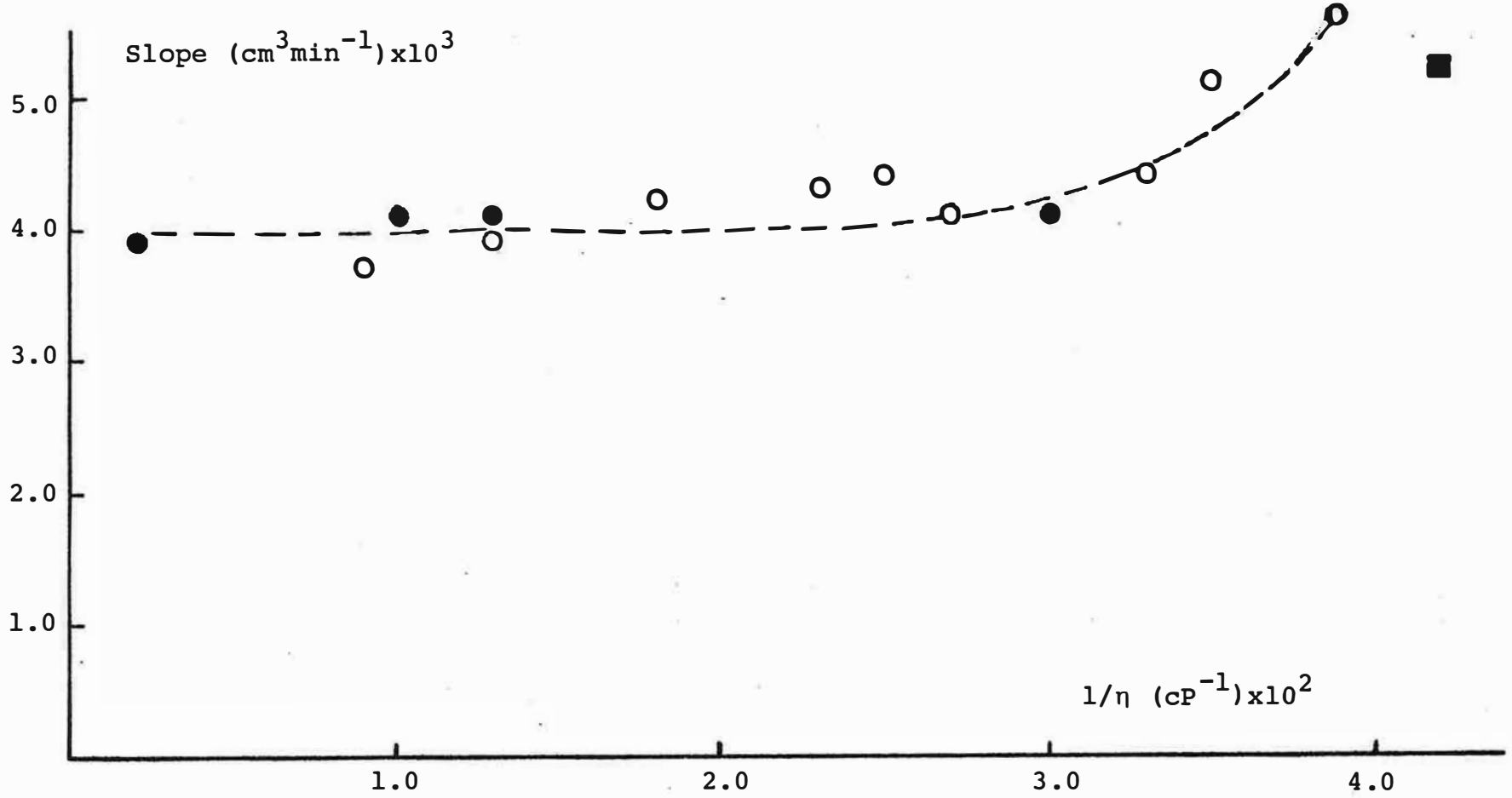


Figure 5.52. Effect of the oil viscosity on salicylic acid release from emulsions. Gelling agent is (●) Aerosil 200, (○) Aerosil 300. (■) Miglyol emulsion with no gelling agent.

irreproducible data, e.g. introduction of the sample into the donor cell might have destroyed the network structure. If the transport of the drug through the interfacial film was the rate-limiting step which was already slow, experiments could not reflect the effect of the oil phase viscosity.

An attempt was made to produce oily gels and emulsions using Bentone 34 and Bentone 38, but these emulsions were unstable during the release experiments giving inconsistent results. Therefore, further investigation was not carried out with these gelling agents.

CHAPTER 6

ASSESSMENT OF STABILITY OF THE EMULSIONS

6.1 Introduction

Some stability tests, such as particle size analysis, electrophoretic mobility, viscosity and creaming rate were carried out in order to predict the stability of the emulsions. The compositions of these emulsions have been given previously in Tables 5.4, 5.22, 5.27, 5.33 and 5.36.

Nine cetomacrogol emulsions (Table 5.4) were stored for long-term stability tests under ambient conditions in order to test for a correlation with the predictions indicated by short-term stability tests. 25±0.2°C was used to represent temperate conditions and 40±0.5°C and below -15°C were chosen to represent the extreme conditions.

6.2 Experimental

6.2.1 Particle size analysis

Emulsions were tested 24 hours after preparation. For long-term stability tests, cetomacrogol emulsions were stored at 25±0.2°C and 40±0.5°C in well closed bottles. The stability tests were performed every day for 1 week, every week for up to 6 weeks, monthly up to 3 months and then at 3-monthly intervals. Before sampling the bottles were inverted gently 20 times to redisperse any creamed droplets with minimal effect on the size distribution.

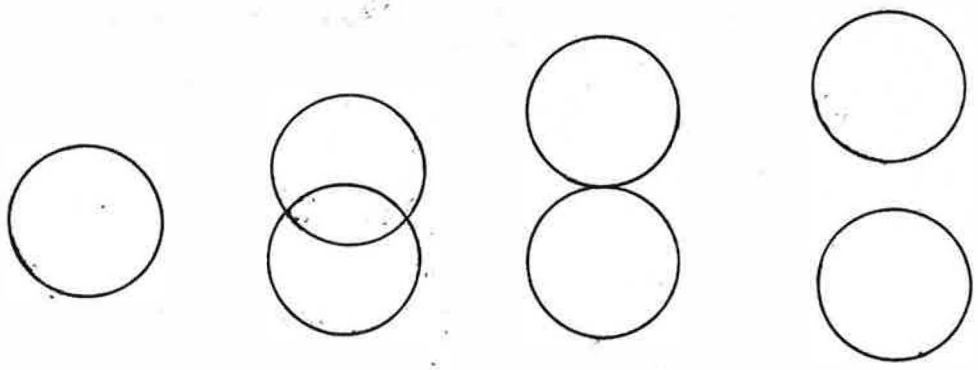
Two methods were used for particle size analysis. A Fleming-Timbrell Double-Image Micrometer (Model A3)

fitted to a Vickers 4-AW microscope was used mainly, but a Joyce Loebl Fotosedimentometer (MK III, Joyce Loebl) was occasionally used as an alternative.

6.2.1.1 Double Image Microscopy

A similar device to that described by Barnett and Timbrell (1962) was used in this study. Two images of one globule can be formed by passing the light through a system of half-silvered mirrors. The images can be sheared relative to each other by application of a small voltage to a solenoid fitted to one half of one of the mirrors. Initially, two images coincide (Figure 6.1a), but as the voltage on the mirror solenoid is increased, the images move apart (Figure 6.1b-d) until they are completely separated. When the two images just touch they have been sheared by an amount equivalent to the diameter of the globule. The voltage required to achieve this separation is a direct measure of the size of the globule and by precalibration the voltage can be presented as a size. Each globule is graded into the appropriate size and is registered on one of ten electromagnetic counters which are operated by a foot switch.

Due to the Brownian motion, emulsions had to be diluted in 40% w/w aqueous glycerin solution to give 50 to 100 globules in the inner area of the eyepiece graticule, and diluted samples were placed in a Thoma haemocytometer cell for counting to minimise distortion of the droplets. Since the droplets were randomly distributed throughout the depth of the cell (100 μm) it was necessary to allow the specimen



(a) (b) (c) (d)

Figure 6.1. Double Image Microscopy.

Table 6.1. Some constants of the viscometer and the cone used.

Torque spring rating	1200 g. cm.
Measured torque	2.0 g. cm. div^{-1} 1960 dyne. cm. div^{-1}
Cone (large)	
Radius	3.5 cm.
Angle - degrees	20'5"
- radians	5.84×10^{-3}
Shear rate constant (Shear rate = RPM x constant)	17.9 s^{-1}
Shear stress constant (Shear stress = scale reading x range x constant)	21.8 dyne cm^{-2}
Viscosity constant (Viscosity = $\frac{\text{Scale reading x range}}{\text{RPM}}$ x constant)	1.2189 Poise

to stand for at least 30 minutes in order to allow the droplets to rise to the top of the cell which could be checked by changing the depth of focus before counting started. It was impossible to accurately size droplets of less than 2 μm diameter and globules smaller than 1 μm could be seen only as diffuse circles if the focus depth of the microscope was altered. Therefore, globules smaller than 1 μm were recorded as being in the size range of 0-1.0 μm. Approximately 500 globules were recorded for each analysis. Although there is disagreement over the minimum number of drops that must be classified, Becher (1965) claims that a count of 300 drops is sufficient to give a size distribution with less than 8 per cent error and to reduce this error to 5 per cent would require the classification of 2690 drops. It is clear from these values that the method is time-consuming and the size distribution may change or drops may move into or out of the field of view due to the Brownian motion during this time. The method did not necessarily detect all of the globules which were smaller than 1 μm in diameter and also it could estimate size as higher than the actual sizes of the particles due to the diffraction effects (Allen, 1981).

6.2.1.2 Photosedimentometer

Due to the difficulty in counting the globules smaller than 1 μm, photosedimentometry was used.

The centrifuge unit of the instrument consists of a disc rotating at a pre-selected speed into which an emulsion sample, previously diluted in an aqueous medium (spin fluid), is injected by means of a syringe. Under the influence of

the centrifugal forces, the oil drops start sedimenting, the rate of sedimentation being determined by their size. Under these circumstances the equation of motion for the drops in the spin fluid is Stokes' law modified for centrifugal sedimentation.

$$Ti = \frac{18\,\eta_s}{\omega^2 D^2 \Delta\rho} \log \frac{R_2}{R_1} \qquad (6.1)$$

where Ti = time elapsed after injection of the sample,

η_s = viscosity of spin fluid,

ω = rotational speed of the disc,

D = particle diameter,

$\Delta\rho$ = density difference between the spin fluid and oil drops,

R_1 = starting radius of the vortex of spin fluid,

R_2 = radius to which particle size settles.

During the centrifugation the optical density of the drops in the white light beam gradually decreases and this is recorded as a function of time. This profile of optical density as a function of time is converted to a drop diameter versus time profile with a computer program. The optical density of a diluted heterodispersed suspension is given by Lothian and Chappel (1951) and Goulden (1958) as

$$\ell n \frac{I_o}{I} = K \sum_{i=1}^{n} Q_i N_i D_i^2 \qquad (6.2)$$

where I_o and I are the intensities of the incident and emergent light beams, K is a constant reflecting the dimensions of the apparatus and globule shape, Q_i is the light scattering coefficient, and N_i is the number of globules of diameter D_i

per unit volume. The optical density resulting from the globule size D_i is given by subtraction,

$$\Delta \ell n \frac{I_o}{I} = \ell n \frac{I_o}{I_1} - \ell n \frac{I_o}{I_{i-1}} = KQ_i N_i D_i^2 \qquad (6.3)$$

The computer program mentioned above utilizes the Q_i values derived by Parkinson et al. (1970) for monodispersed suspensions of poly(methylmethacrylate) spheres with different sizes and calculated the particle size distribution on various bases (number, length, area and volume bases). The theory and the analysis of the data has been given in detail by Matsumoto and Fukushima (1974) and Groves, Kaye and Scarlett (1964).

The disc was set spinning at a selected speed of 3000 rpm and 30 ml of a diluted emulsion suspension (in distilled water) was injected via the entry port. The chart recording of OD/time was converted to a globule diameter/time relationship and the globule size distribution was evaluated with the computer program.

6.2.2 Rheological testing

Rheological tests were carried out using a Ferranti-Shirley cone and plate continuous shear viscometer (Ferranti Ltd., Moston, Manchester). Some constants of the instrument are listed in Table 6.1.

The cone-plate gap was set with the cone rotating at 5 rpm. The correct gap setting was obtained when the application of slight upward pressure to the plate caused a deflection on the meter which returned to zero as soon as

the pressure was removed (Davies, 1982). Approximately 1 ml of sample was placed on the centre of the plate by means of a glass tube and the plate was raised to its operating position. The sample was tested in the automatic mode of operation and flow curves were recorded with a Bryans 29050 X-Y/t A3 plotter (Model No. MR-154H, Bryans Southern Instruments Ltd., Mitcham, Surrey). A sweep time of 240 seconds was used to reach a maximum cone-speed of 100 rpm or 1000 rpm, because even with Newtonian fluids sweep times of less than 120 seconds produce traces with measurable hysterisis caused by inertial effects due to the acceleration of the cone (Davies, 1982). The measurements were made at 25°C and the results quoted in the text are always the calculated viscosities at the maximum speed of 100 rpm or 1000 rpm, in other words at shear rates of 1790 sec^{-1} or 17900 sec^{-1}.

6.2.3 Electrophoretic mobility measurements

The objective of these experiments was to determine to what extent the charge on the droplets changed during storage, and how the charge was related to the stability of the emulsions and changed by the nature of the surfactant.

In microelectrophoresis, a potential gradient is applied along a capillary, and the drops move under the influence of two effects.

1. Motion of the drops relative to the continuous phase - the electrophoretic effect.
2. Motion of the continuous phase relative to the charged walls of the glass tube - electroosmotic effect.

The continuous phase moves in one direction along the walls of the tube and returns along the centre which results in a variation of drop velocities across the diameter of the tube. Electrophoretic mobility of the drops must be measured at the layer between the two streams of liquid which is known as the stationary layer. Lamb (1888) stated that this layer is located at 0.293 R from the wall or 0.707 R from the axis of the tube, where R is the radius of the tube. Since the electroosmotic mobility at this layer is zero, the measured velocity of the droplets will be their true electrophoretic mobility.

The apparatus used was a Microelectrophoresis Apparatus, Mark I (Rank Bros., Bottisham, Cambridge) fitted with a capillary cell with electrodes of grey platinum. The apparatus has been described by Bangham et al. (1958). The cell was located in a thermostatted waterbath which simplified the temperature control. Errors can arise when focussing the microscope on the stationary layer in a cell of circular cross-section (Henry, 1938). However, because the optical window thickness was not more than 100 μm and the objective was also immersed in water, the error caused by the difference in the refractive indices became negligible (Bangham et al., 1958).

The electrophoretic mobility at the stationary level is calculated by the following equation:

$$\mu = \frac{n}{T} \cdot \frac{L_e L_d}{V} \qquad (6.4)$$

where n = number of graticule divisions for which measurements were taken,

L_d = the length of one graticule division (μm),

L_e = the effective electrical length between the electrodes (cm),

T = time (sec.),

V = the applied voltage (V).

The electrical field length, L_e, is the distance in the capillary tube between the electrodes and is calculated by

$$L_e = \frac{KV\pi R^2}{I} \qquad (6.5)$$

where K = the specific conductivity of KCl solution used (Siemens cm^{-1}),

V = the potential applied (V),

R = the inside radius of the capillary tube (cm),

I = the current (amps.).

6.2.3.1 Determination of the capillary tube diameter

The cell was cleaned with chromic acid for 3 hours and rinsed thoroughly with large amounts of distilled water, and then filled with a 0.2% w/v aqueous methylene blue solution. By moving the cell, the microscope was focussed on the upper inner surface of the cell, which was easily recognizable due to both the colour of the solution and the imperfections in the glass, and the micrometer reading was noted. The cell was then moved upwards to bring the lower inner surface of the cell into focus and the micrometer was read. The diameter of the cell was the difference between the two micrometer readings. Lamb's (1888) value of 0.293 R from the inner wall of the tube was used to locate the stationary layer.

6.2.3.2 Measurement of the effective electrical length of the cell

The current was measured at 25°C when 0.001 M, 0.01 M, 0.1 M and 1 M KCl solutions were placed in the capillary tube and a known potential difference was applied. A mean value of L_e was then calculated from equation (6.5).

6.2.3.3 Calibration of the graticule

The chessboard eyepiece graticule was calibrated by a stage micrometer slide which was placed on the capillary tube holder while immersed in water.

6.2.3.4 Preparation of the electrodes

Prior to platinization, the surface of the electrodes was cleaned with a fine emery paper and water in order to remove previous colloidal platinum coatings. The water wash was followed by rinsing with acetone and a solution of two parts by volume of 95% alcohol, one part acetone and one part methyl alcohol, and finally with absolute alcohol. The electrodes then were placed in platinizing solution, which was an aqueous solution of chloroplatinic acid and lead acetate, and connected to the power pack of the apparatus. A current of 10 mA/cm^2 was passed through the solution as described by Ferris (1974). By reversing the polarity at 5 minute intervals the process was continued over a period of 40 mins. until the electrodes had collected a fine grained velvety black coating. Although applying a low current density requires a long plating duration, it does provide a good surface coating (Ferris, 1974). After the electrodes

have been prepared, they were placed in distilled water and were connected to form a short circuit for several days until the charge produced by the platinizing procedure had decayed. Electrodes coated with black platinum were then heated as described by Whetham (1900) to give a grey platinum coating which reduces the possibility of absorption of the ions on to the electrodes during the measurements.

6.2.3.5 Procedure for measuring the electrophoretic mobility of the globules

The emulsions were always diluted in distilled water to give a dilution of about 0.02% of the oil phase. The cell was always cleaned thoroughly and rinsed several times with distilled water and rinsed with the test solution at least twice. The cell was then filled with the test solution and the electrodes were inserted to exclude any air bubbles. The microscope was focussed on the stationary level and approximately 20 drops were timed with a stopwatch having 0.1 second divisions, at both positive and negative polarities. Various potential differences were applied in order to check whether the mobility was independent of the applied potential and the stationary level was located correctly.

6.2.4 Measurement of the creaming rate

The nine cetomacrogol emulsions (Table 5.4) were kept in 25 ml graduated cylinders with tight stoppers at 25±0.2°C and relative cream volume was measured. The relative cream volume was calculated by dividing the cream volume by that of the total emulsion.

6.2.5 Freezing-thawing experiments

Cetomacrogol emulsions (Table 5.4) were exposed to low temperatures, below -15°C, in a freezer for up to 6 months and at predetermined intervals left at room temperature to thaw. The amount of the phases separated was measured and the percentage of these were calculated. Cycling of the samples between the two extremes of temperatures, 40°C and below -15°C, was planned initially, but since on thawing cracking of the emulsions was observed, this was thought to be unnecessary.

6.3 Results and discussion

6.3.1 Particle size analysis

The results obtained by both methods, Double Image Microscopy and Photosedimentometry, are given in Tables 6.2-6.8. Although the emulsions prepared with cetomacrogol (Table 5.4) were tested for up to 6 months at predetermined intervals, by microscopy, only two tables are presented (Tables 6.2 and 6.3) in order to show the effect of ageing and the storage conditions due to the similar results obtained from the analysis. As can be seen from these tables, although there were some variations in the results, no significant change in the size distribution was observed. The variation was only attributed to the experimental error. During the course of the study, the reliability of the particle size distribution by optical microscopy was suspected, because a large number of particles were in the region of uncertainty (less than 1 μm) and probably many more of the globules could not be detected. This was confirmed by using the disc centrifuge (Table 6.4)

Table 6.2. Particle size distribution of emulsions, after 1 day storage at 25°C and 40°C as percent number within size ranges (μm) shown, determined by microscopy.

μm / No.	Storage conditions												
	25±0.2°C							40±0.5°C					
	0-1.0	1.0-2.0	2.0-3.0	3.0-4.0	4.0-5.0	5.0-6.0	>6.0	0-1.0	1.0-2.0	2.0-3.0	3.0-4.0	4.0-5.0	> 5.0
II-1	87.05	10.72	1.94	0.28	-	-	-	86.27	11.27	1.96	0.49	-	-
II-2	86.18	10.10	2.72	0.25	0.25	-	0.5	83.89	14.77	1.01	0.34	-	-
II-3	85.41	7.71	5.90	0.98	-	-	-	86.49	9.49	3.29	0.73	-	-
II-4	88.77	10.14	1.10	-	-	-	-	91.53	8.14	0.33	-	-	-
II-5	85.53	12.83	1.32	0.33	-	-	-	88.22	9.62	1.44	0.72	-	-
II-6	84.65	12.11	1.77	1.47	-	-	-	86.49	11.35	2.16	-	-	-
II-7	82.63	16.73	0.45	0.22	-	-	-	85.96	11.58	2.22	0.25	-	-
II-8	93.98	5.12	0.89	-	-	-	-	93.75	5.83	0.42	-	-	-
II-9	85.63	12.40	1.73	0.25	-	-	-	28.90	6.73	3.37	1.01	-	-

Table 6.3. Particle size distribution of emulsions after 6 months storage at 25±0.2°C and 40±0.5°C as percent number within size ranges (μm) shown, determined by microscopy.

μm / No.	Storage conditions												
	25±0.2°C							40±0.5°C					
	0-1.0	1.0-2.0	2.0-3.0	3.0-4.0	4.0-5.0	5.0-6.0	>6.0	0-1.0	1.0-2.0	2.0-3.0	3.0-4.0	4.0-5.0	>5.0
II-1	87.17	10.86	1.96	0.01	-	-	-	87.00	10.50	2.00	0.28	0.22	-
II-2	88.66	10.39	0.93	0.02	-	-	-	85.41	7.73	5.88	0.90	0.08	-
II-3	86.49	11.35	2.16	-	-	-	-	85.43	12.53	1.42	0.50	0.12	-
II-4	87.77	10.14	1.60	0.5	-	-	-	88.50	10.22	1.10	0.18	-	-
II-5	88.22	9.42	1.44	0.72	0.20	-	-	88.90	6.53	3.43	1.01	0.13	-
II-6	86.29	9.39	3.30	0.73	0.20	0.09	-	90.73	8.27	0.29	0.50	0.21	-
II-7	85.90	11.40	2.37	0.26	0.07	-	-	86.49	9.29	3.33	0.79	0.10	-
II-8	88.77	10.01	1.05	0.10	0.07	-	-	90.65	7.83	0.53	0.56	0.43	-
II-9	86.27	10.27	2.56	0.52	0.38	-	-	88.22	8.50	1.52	1.47	0.30	-

Table 6.4. Effect of the age and storage condition on particle size distribution of the emulsions by Joyce Loebl photosedimentometer.

Emulsion No.	Age (weeks)	Storage temp.°C	Percent number per μm interval, and mean volume diameter, d_{vs} (μm)											
			0.175	0.225	0.275	0.325	0.375	0.425	0.475	0.550	0.650	0.750	>0.850	d_{vs}
II-1	10.0	25±0.2	79.20	15.21	3.96	1.04	0.36	0.13	0.05	0.04	0.01	0.01	-	0.197
II-2	9.5	25±0.2	81.45	13.59	3.59	0.90	0.28	0.09	0.05	0.03	0.01	0.01	-	0.194
II-3	9.0	25±0.2	75.77	17.23	4.91	1.31	0.45	0.17	0.09	0.05	0.02	0.01	-	0.201
II-1	27.5	25±0.2	80.33	14.14	3.86	1.08	0.33	0.14	0.06	0.04	0.01	0.01	-	0.197
II-1	27.5	40±0.5	79.48	14.72	4.07	1.08	0.38	0.13	0.07	0.05	0.02	0.01	-	0.198
II-2	27.0	25±0.2	80.58	14.20	3.72	0.94	0.34	0.13	0.05	0.03	0.01	0.01	-	0.202
II-3	26.5	25±0.2	78.64	16.31	0.74	3.35	0.54	0.23	0.10	0.07	0.02	0.01	-	0.202
II-3	26.5	40±0.5	74.73	17.41	5.34	1.55	0.56	0.21	0.09	0.07	0.02	0.01	-	0.204

in that the globules were less than 1 μm, mean diameter, d_{vs}, being around 0.2 μm. Groves et al. (1975 a,b), Matsumoto et al. (1974), Sherman and Benton (1980) have stated that, in many emulsified systems, large numbers of globules are actually in the submicrometer range and suggested that the centrifugal methods may provide the best results; however, the interpretation of the results appear to be complicated. Groves et al. (1968) compared the methods available for particle sizing and concluded that either the electron microscope or a photosedimentometer could be used to size particles in the submicrometer range. The electron microscope presents difficulties due to the local heating effects of the electron beam, the effect of drying under vacuum and the necessity to measure a sufficient number of particles for statistical accuracy (Groves et al., 1968). The centrifugal photosedimentometer also presents a number of difficulties in the interpretation of the results and generally over-emphasizes the finer particles in a given system (Groves and Yalabik, 1975; Groves and Freshwater, 1968). However, by calibration of the instrument by using corrections due to light-scattering coefficients of the small particles, realistic size distribution data can be obtained (Groves et al., 1968). The computer program used during the analysis utilizes the light-scattering coefficients determined by Parkinson et al. (1970). A typical computer output is given in Appendix IV, and the percent cumulative undersize on number, length, surface area and volume bases against the globule diameter is plotted in Figure 6.2 for Emulsion II-1. Due to the similarity of the data for other emulsions, only

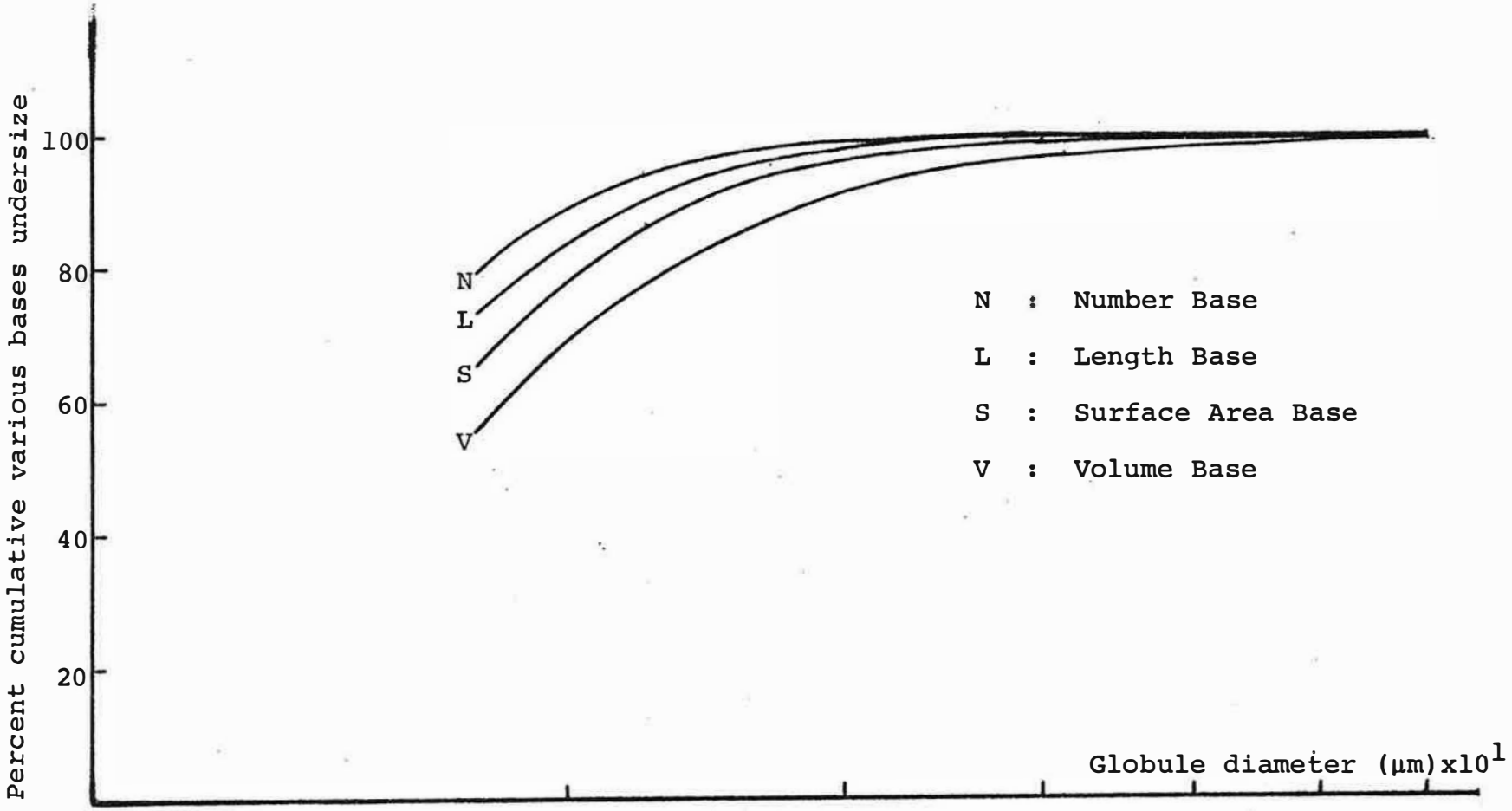


Figure 6.2. A typical size distribution of emulsions on various bases.

tables showing percent by number per μm interval and mean volume diameter, d_{vs}, are presented. Tables 6.5 and 6.6 compare the particle size distribution data of cetomacrogol emulsions stored at 25±0.2°C and 40±0.5°C for 1 year. Both tables clearly indicate that these emulsions were very stable. Although accelerated stability tests, such as exposure to high or low temperatures, might affect the stability in a number of ways, Bennett et al. (1968) state that "An increase of 10°C in the temperature is considered to double the rate of most reactions. Therefore 3 months at 45-50°C is equivalent to one year at 20-25°C for many systems." Regarding this statement, the cetomacrogol emulsions at every surfactant concentration and phase volume ratio, were stable even when stored at 40±0.5°C for 1 year.

Emulsions prepared with CTAB (III-1) and SLS (III-2) again showed a similar particle size distribution with both methods (Tables 6.7 and 6.8). Although long-term stability tests were not carried out, these emulsions were predicted to be stable from their size distribution. On the other hand, emulsions stabilized with Tween 20/Span 80 mixtures (III-4 to III-11 as given in Table 5.22) exhibited somewhat different size distributions with both methods (Tables 6.7 and 6.8). Tween 20/Span 80 mixtures produced emulsions with smaller globule sizes than Tween 20 or Span 80 alone. At HLB values of less than about 6, the emulsions contained bigger globules and at HLB 4.3, Span 80 alone produced an emulsion which was unstable, oil separation being observed on the second day. Emulsion III-12 and III-13 which were prepared from Tween 20: Span 80 at a ratio of 4:1, were also stable having similar

Table 6.5. Effect of ageing on particle size distribution of the emulsions by Joyce Loebl photosedimentometer. Emulsions were kept at 25±0.2°C for 1 year.

Emulsion No.	Percent number per μm interval, and mean volume diameter d_{vs} (μm)													
	0.175	0.225	0.275	0.325	0.375	0.425	0.475	0.550	0.650	0.750	0.850	0.950	>1.100	d_{vs}
II-1	79.68	14.42	4.07	1.14	0.39	0.15	0.07	0.04	0.02	0.01	0.01	-	-	0.198
II-2	81.44	13.52	3.61	0.94	0.29	0.11	0.05	0.03	0.01	-	-	-	-	0.195
II-3	76.53	15.95	4.99	1.58	0.54	0.20	0.10	0.07	0.02	0.01	0.01	-	-	0.203
II-4	87.36	9.64	2.11	0.57	0.19	0.07	0.03	0.02	0.01	-	-	-	-	0.189
II-5	89.85	6.61	2.63	0.64	0.16	0.06	0.02	0.02	0.01	-	-	-	-	0.187
II-6	67.87	27.86	1.92	1.85	0.23	0.07	0.02	0.09	0.05	0.02	0.01	0.01	-	0.204
II-7	81.99	13.27	3.40	0.87	0.27	0.10	0.05	0.03	0.01	0.01	-	-	-	0.194
II-8	81.87	13.51	3.38	0.83	0.24	0.08	0.04	0.02	0.01	0.01	0.01	-	-	0.194
II-9	86.09	11.10	2.29	0.42	0.06	0.01	-	0.02	0.01	0.01	-	-	-	0.188

Table 6.6. Effect of ageing on particle size distribution of the emulsion by Joyce Loebl photosedimentometer. Emulsions were kept at 40±0.5°C for 1 year.

Emulsion No.	Percent number per μm interval, and mean volume diameter, d_{vs} (μm)													
	0.175	0.225	0.275	0.325	0.375	0.425	0.475	0.550	0.650	0.750	0.850	0.950	>1.100	d_{vs}
II-1	80.33	14.14	3.86	1.08	0.33	0.14	0.06	0.04	0.01	0.01	-	-	-	0.197
II-2	83.90	11.73	2.96	0.89	0.28	0.12	0.05	0.04	0.01	0.01	0.01	-	-	0.194
II-3	76.53	15.85	4.99	1.68	0.54	0.20	0.10	0.07	0.02	0.01	0.01	-	-	0.203
II-4	82.78	13.04	2.93	0.81	0.25	0.10	0.04	0.03	0.01	0.01	-	-	-	0.193
II-5	69.93	23.74	4.59	1.11	0.36	0.14	0.06	0.05	0.01	0.01	-	-	-	0.203
II-6	76.53	15.95	4.99	1.58	0.54	0.20	0.10	0.06	0.02	0.01	0.01	0.01	-	0.203
II-7	84.43	11.64	2.91	0.71	0.18	0.07	0.03	0.02	0.01	0.01	-	-	-	0.191
II-8	81.44	13.52	3.61	0.94	0.29	0.11	0.05	0.03	0.01	-	-	-	-	0.195
II-9	80.48	13.81	4.02	1.06	0.36	0.14	0.06	0.04	0.02	0.01	-	-	-	0.197

Table 6.7. Particle size distribution of emulsions by microscopy. Emulsions were kept at 25±0.2°C for 1 day.

Emulsion	Percent number within the size range (μm) of						
	0-1.0	1.0-2.0	2.0-3.0	3.0-4.0	4.0-5.0	5.0-6.0	6 <
III-1	94.66	4.00	1.33	-	-	-	-
III-2	90.28	8.50	0.81	0.40	-	-	-
III-3	93.98	5.12	0.89	-	-	-	-
III-4	85.01	15.86	2.24	0.94	0.35	0.12	0.47
III-5	88.71	10.37	0.46	0.23	-	-	0.23
III-6	91.85	7.59	-	0.37	0.19	-	-
III-7	88.80	10.13	0.27	0.53	0.27	-	-
III-8	82.18	14.38	2.19	0.63	0.63	-	-
III-9	73.69	17.27	5.22	2.41	0.80	-	0.40
III-10	14.12	37.65	25.88	9.41	5.80	3.53	3.53
III-11	9.52	30.46	35.75	10.57	8.20	4.20	1.30
III-12	95.00	4.44	0.55	-	-	-	-
III-13	92.85	6.50	0.33	0.32	-	-	-

Table 6.8. Particle size distribution of emulsions by Joyce Loebl photosedimentometer. Emulsions were kept at 25±0.2°C for 1 day.

Emulsion	Percent number per μm interval, and mean volume diameter, d_{vs} (μm)														
	0.175	0.225	0.275	0.325	0.375	0.425	0.475	0.550	0.650	0.750	0.850	0.950	1.100	1.100<	d_{vs}
III-1	58.59	30.07	8.21	2.03	0.67	0.24	0.10	0.07	0.02	0.01	-	-	-	-	0.215
III-2	82.11	13.35	2.29	0.82	0.27	0.11	0.03	0.01	0.01	-	-	-	-	-	0.195
III-3	84.15	11.99	2.79	0.66	0.22	0.10	0.04	0.03	0.01	0.01	-	-	-	-	0.192
III-4	73.09	18.99	5.50	1.57	0.48	0.21	0.08	0.05	0.02	0.01	0.01	-	-	-	0.204
III-5	86.09	10.96	2.62	0.00	0.19	0.10	0.01	0.02	0.01	-	-	-	-	-	0.189
III-6	85.43	10.64	2.91	0.71	0.18	0.07	0.03	0.02	0.01	-	-	-	-	-	0.191
III-7	76.82	16.44	4.91	1.23	0.33	0.13	0.05	0.03	0.01	-	-	-	-	-	0.200
III-8	79.93	14.30	3.91	1.15	0.44	0.17	0.06	0.03	0.01	-	-	-	-	-	0.197
III-9	0.00	40.19	40.18	11.96	4.40	1.68	0.79	0.53	0.16	0.07	0.01	0.02	0.01	-	0.287
III-10	0.00	0.00	40.97	29.91	13.54	7.03	3.66	2.99	1.16	0.42	0.19	0.09	0.07	-	0.366
III-12	83.06	12.93	2.98	0.68	0.20	0.08	0.03	0.02	0.01	0.01	-	-	-	-	0.192
III-13	83.17	12.83	2.83	0.70	0.20	0.15	0.04	0.03	0.01	0.01	-	-	-	-	0.192

size distributions to that of Emulsion III-6.

6.3.2 Electrophoretic mobility measurements

Electrophoretic mobilities were determined at 25°C and are reported in Tables 6.9, 6.10 and 6.11. Except for Emulsion III-1, all droplets were negatively charged. Since the mobility of the globules does not change with the applied potential, the relationship between the velocity or mobility and the potential gradient was checked each time (Sherman, 1968). The observed linear relationship between the drop velocity and the potential gradient also indicated that the location of the stationary level was right. The liquid paraffin emulsion globules prepared by the method described by Powney and Wood (1940) had a mobility of -3.46 (standard error = 0.05 and P = 0.99) which agreed with the literature values of -4.35 (Powney and Wood, 1940), -3.6 (Ginn et al., 1964) and -3.74 (Davis, 1967). Electrophoretic mobility of the Miglyol globules dispersed in distilled water without a stabilizer was -2.95 (SE = 0.09 at P ≈ 0.99).

Table 6.9 summarizes the effect of time and storage conditions on the mobility of cetomacrogol emulsion droplets. Although there was variation observed between the mobility of the emulsions as well as the mobilities determined for one emulsion, this was not significant. Garvey et al. (1976) and Elworthy and Florence (1967) reported that a reduction in the zeta potential is related to the adsorbed layer thickness of non-ionic materials adsorbed but the stability would not be predicted. All nine emulsions consisted of globules having the similar mobilities indicating that the thickness

Table 6.9. Effect of storage conditions and time on electrophoretic mobility ($\mu ms^{-1}V^{-1}cm^{-1}$) of the emulsion droplets stabilized with cetomacrogol. Results are given as mean ± limits of error at P = 0.99, and are negatively charged.

Emulsion No.	Storage conditions									
	25±0.2°C					40±0.5°C				
	1 day	1 week	6 weeks	3 months	6 months	1 day	1 week	6 weeks	3 months	6 months
II-1	2.39±0.07	2.42±0.05	2.39±0.06	2.32±0.08	2.38±0.08	2.39±0.05	2.27±0.11	2.22±0.11	2.26±0.11	2.47±0.14
II-2	2.33±0.06	2.34±0.06	2.23±0.11	2.29±0.11	2.29±0.11	2.40±0.11	2.34±0.07	2.22±0.11	2.40±0.06	2.36±0.06
II-3	2.12±0.09	2.21±0.08	2.37±0.03	2.24±0.07	2.31±0.06	2.07±0.09	2.36±0.03	2.25±0.07	2.24±0.07	2.32±0.06
II-4	1.98±0.07	2.47±0.06	2.46±0.06	2.33±0.10	2.20±0.14	2.21±0.11	2.26±0.11	2.27±0.11	2.21±0.13	2.27±0.14
II-5	2.26±0.10	2.34±0.09	2.19±0.09	2.29±0.11	2.33±0.06	2.20±0.09	2.30±0.10	2.23±0.08	2.33±0.06	2.31±0.08
II-6	2.07±0.10	2.18±0.11	2.25±0.07	2.21±0.08	2.33±0.09	2.33±0.08	2.11±0.09	2.46±0.13	2.30±0.08	2.34±0.09
II-7	2.09±0.11	2.40±0.06	2.32±0.08	2.23±0.14	2.24±0.07	2.24±0.07	2.27±0.11	2.40±0.07	2.29±0.11	2.33±0.10
II-8	2.40±0.10	2.41±0.10	2.29±0.11	2.02±0.05	2.25±0.07	2.36±0.06	2.37±0.06	2.22±0.11	2.31±0.08	2.21±0.11
II-9	2.10±0.09	2.19±0.11	2.39±0.11	2.25±0.08	2.19±0.09	2.19±0.09	2.36±0.06	2.43±0.06	2.27±0.12	2.25±0.07

Table 6.10. Effect of the nature of the surfactant on electrophoretic mobility (mean ± limits of error at P = 0.99) and viscosity. Except for Emulsion III-1 all drops are negatively charged.

Emulsion No.	Electrophoretic mobility $\mu ms^{-1}V^{-1}cm^{-1}$, at 25°C	Viscosity cP, at 25°C
III-1	(+)4.69±0.19	8.59
III-2	2.51±0.09	8.22
III-3	2.28±0.07	10.18
III-4	3.05±0.17	10.30
III-5	3.41±0.16	11.40
III-6	2.97±0.18	12.43
III-7	2.90±0.14	11.09
III-8	3.12±0.15	10.60
III-9	3.01±0.25	9.20
III-10	2.79±0.11	7.74
III-11	2.92±0.13	6.76
III-12	2.93±0.14	15.78
III-13	2.71±0.17	18.59

Table 6.11. Effect of the gelling agents on electrophoretic mobility (mean ± limits of error at P = 0.99). All drops are negatively charged.

Emulsion No.	Electrophoretic mobility $\mu ms^{-1}V^{-1}cm^{-1}$
V-1	1.78±0.12
V-2	1.83±0.16
V-3	0.93±0.08
V-4	1.62±0.16
VI-1	2.09±0.09
VI-2	1.28±0.25
VI-3	1.44±0.25
VI-4	1.28±0.16
VII-1	2.64±0.32
VII-2	2.70±0.09
VII-3	2.22±0.13
VII-4	2.22±0.19
VII-5	2.04±0.11
VII-6	2.19±0.09
VII-7	2.05±0.11

of the cetomacrogol layer did not change with the surfactant concentration. Storage conditions and ageing did not affect the mobilities indicating that the surfactant film therefore the emulsions were stable.

A minimum zeta potential of 30 mV is considered necessary to stabilize an emulsion (Kitchener and Musselwhite, 1968). Current results show that although Miglyol globules in water had zeta potentials above this value, they did not form a stable emulsion. Similarly, Emulsion III-11 did not form a stable emulsion but the zeta potential was higher than the stated necessary value. However, as shown in Tables 6.10 and 6.11, the nature of the surfactant affected both the charge and the magnitude of the mobilities. Absorption of CTAB molecules onto the globules produced a positive charge, whilst SLS and non-ionic emulsifiers produced negatively charged drops. The gelling agents did not change the charge of the globules which were stabilized with cetomacrogol, but affected the magnitude of the mobility. This probably suggests a change in the interfacial film, a change in the packing of the cetomacrogol molecules or the presence of silicon dioxide molecules together with cetomacrogol molecules.

6.3.3 Rheological examination of the emulsions

As shown in Table 6.12, the viscosities of the cetomacrogol emulsions did not change with time under the storage conditions studied. These results agreed well with the particle size and mobility determinations that cetomacrogol emulsions were very stable. Increasing concentrations of the oil phase and the surfactant increased the viscosities. However, all

Table 6.12. Effect of ageing and storage conditions on viscosity (cP) of emulsions. Measurements were taken at 25°C and the viscosities were calculated at 1000 rpm (shear rate 1790$0$ sec^{-1}).

Emulsion No.	Storage conditions									
	25±0.2°C					40±0.5°C				
	1 day	1 week	6 weeks	3 months	6 months	1 day	1 week	6 weeks	3 months	6 months
II-1	2.07	2.13	2.07	2.13	1.98	2.07	1.89	1.95	1.89	2.07
II-2	6.61	5.73	5.85	5.73	5.60	6.67	5.24	5.24	5.73	5.85
II-3	28.03	24.87	22.48	27.42	27.06	28.09	28.03	27.42	25.48	22.61
II-4	2.07	2.80	2.07	2.19	2.13	2.07	2.04	2.01	2.07	2.07
II-5	7.37	6.16	5.42	6.09	5.97	7.03	5.61	5.55	5.42	6.00
II-6	27.06	33.78	30.59	28.03	32.72	27.49	33.52	32.30	28.03	30.59
II-7	2.86	2.77	2.59	2.62	2.68	2.79	2.56	2.59	2.59	2.62
II-8	7.86	7.80	8.10	7.68	7.92	7.80	7.68	7.92	8.10	7.49
II-9	45.10	39.98	45.95	38.64	40.05	40.71	39.91	42.12	38.64	40.03

emulsions exhibited shear thickening (antithixotropic) properties as shown in Figure 6.3.

Although the nature of the surfactant did not change the viscosity of the emulsions significantly, there was a slight but steady reduction in viscosity when decreasing HLB values of Tween 20/Span 80 mixtures were used as emulsifiers (Table 6.10). This could be attributed to the increased globule size of the emulsion (Sherman, 1960; Matsumoto and Sherman, 1969; Parkinson et al., 1970). In addition, the nature of the adsorbed emulsifier film can affect the rheological properties of an emulsion (Kirikou, Sherman, 1979). Emulsion III-12 and III-13 showed greater viscosities than Emulsion III-6 which was due to the increased concentration of the surfactant.

6.3.4 Freezing-thawing experiments

Table 6.13 shows the percent separated phases of the emulsion on thawing. Although complete separation of two phases was never observed, freezing caused the emulsions to break. This experiment did not contribute to the stability tests very much, but clearly indicated that emulsions were not stable when frozen, and could not return to the original form on thawing.

Similarly, creaming rate experiments did not show any measurable separation. There was no phase separation observed, and because the emulsions were very opaque even after some creaming, the boundary between the creamed layer and dilute emulsion was impossible to see.

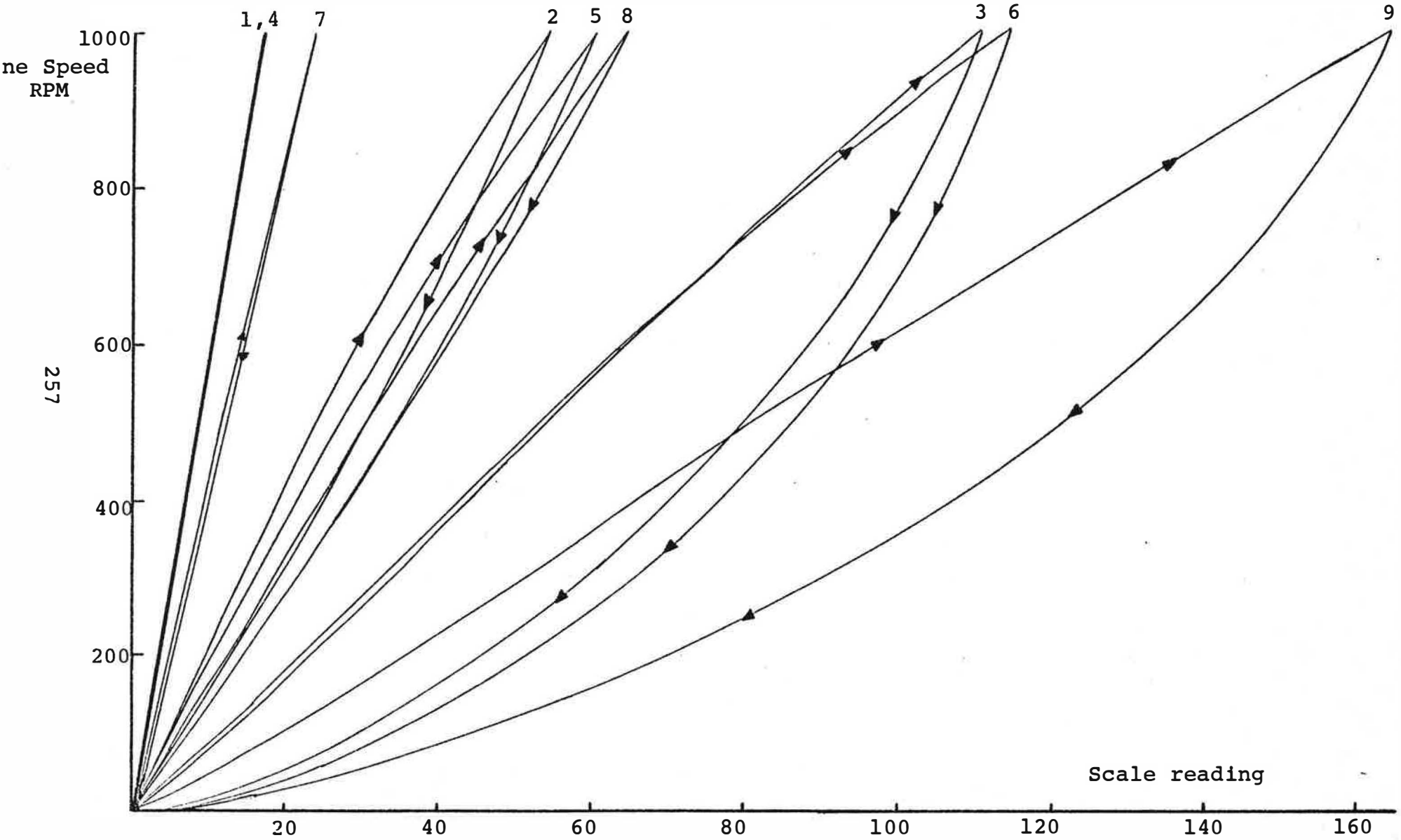


Figure 6.3. Rheograms of the Emulsions II-1 to II-9 at 25°C. Numbers on the rheograms represent the emulsion number.

Table 6.13. Effect of freezing time on percent of the separated phases after thawing of the emulsions.

Emulsion No.	TIME														
	1 day			1 week			6 weeks			3 months			6 months		
	Oil	Coarse emulsion	Turbid aqueous	Oil	Coarse emulsion	Turbid aqueous	Oil	Coarse emulsion	Turbid aqueous	Oil	Coarse emulsion	Turbid aqueous	Oil	Coarse emulsion	Turbid aqueous
II-1	-	26.79	73.21	-	30.27	69.73	-	25.64	74.36	-	27.45	72.55	20.51	5.13	74.36
II-2	-	45.94	54.05	-	62.30	37.70	37.04	9.88	53.09	29.03	16.13	54.84	34.14	12.20	53.66
II-3	-	54.29	30.00	-	77.78	32.22	52.98	8.33	38.89	57.58	9.09	33.33	42.86	25.71	31.43
II-4	-	27.96	72.09	-	37.5	62.5	-	23.81	76.19	-	31.25	68.75	14.29	11.90	73.81
II-5	-	47.69	52.31	20.83	20.83	58.33	34.29	8.57	57.14	30.00	20.00	50.00	33.73	13.35	52.92
II-6	59.46	5.41	35.14	54.17	8.33	37.50	43.24	24.32	32.43	51.73	6.89	41.38	43.98	25.25	30.77
II-7	-	28.57	71.43	-	33.33	66.67	14.76	19.05	66.19	13.33	20.00	66.67	10.26	15.38	74.36
II-8	-	53.85	46.15	10.00	43.85	46.15	21.58	23.16	55.26	22.92	26.34	50.74	25.64	23.08	51.28
II-9	9.68	64.52	25.81	10.0	58.00	32.00	12.08	58.91	29.02	13.91	60.00	26.09	13.33	60.00	26.67

It can therefore be seen that with the exception of emulsions stabilized with Tween-Span mixtures of low HLB, all of the emulsions were stable. Particle size analysis indicated that optical microscopy was not a sufficiently sensitive method to use for these emulsions since a large number of particles were in the submicron range.

CHAPTER 7

CONCLUSIONS AND SUGGESTIONS FOR FURTHER WORK

7.1 Conclusions

The studies reported in this thesis have indicated that emulsions can be used as sustained-release drug delivery systems and the release characteristics of an emulsion can be changed by a number of factors.

The ternary phase diagrams carried out with anionic (sodium lauryl sulphate), cationic (cetrimide) and non-ionic (cetomacrogol-1000) surfactants indicated that Miglyol 812 is a suitable oil to produce stable emulsions.

The release rate of the model drug, salicylic acid, was the fastest from the aqueous solution. However, this could be altered by micellar solubilization of the drug in aqueous surfactant solutions. The inverse relationship observed between the surfactant concentration and the release rates was shown to be due only to the reduced non-micellar drug concentration.

The release was slow from the oily solution suggesting that this might control the drug transport from the oil to the aqueous phase and, therefore, release from the emulsion. However, the results showed that when the oil concentration of the emulsion was high, release was the slowest, despite the total surface area being increased considerably due to the emulsification. This clearly indicated the existence of a barrier to drug release in the form of an interfacial film as suggested earlier (Higuchi, 1964; Goldberg et al.,

1969; Ghanem et al., 1969 and 1970; Surpuriya et al., 1972a; Gatmaitan et al., 1977). Further studies proved that when different surfactants were used to stabilize emulsions having the same oil/water phase volume ratios, the release was affected due to a change in the interfacial barrier.

The experiments designed to demonstrate the effect of the phase-volume ratio and the apparent partition coefficient showed that there was an inverse relationship between the phase-volume ratio and the release rate as expected (Ghanem et al., 1970b), although micellar phase concentration affected it only when the pH was increased. Surpuriya et al. (1972a) reported that in the sodium taurocholate-lecithin stabilized system, changing the concentration but keeping the ratio of these constant, had almost no effect on the permeability coefficient for cholesterol and desmosterol. However, there was a direct proportionality between the free-drug and the permeability coefficient when sodium lauryl sulphate was present. Gatmaitan et al. (1976) also observed similar results in their studies. Nevertheless, Surpuriya et al. (1972b) did show that when the lecithin-bile salt ratio was increased while keeping the bile salt concentration constant, interfacial permeability coefficients of the sterols decreased. McNulty (1975) related the observed differences in the transport rates to the change in the apparent partition coefficient. In the present study, although the apparent partition coefficient of salicylic acid changed with the concentration

of the surfactant, micellar phase was not directly involved in the release. However, it influenced the extent of the drug distribution in the phases and affected the overall release from the emulsions when the pH was high. The observed effect of pH is also important with respect to administration, since it suggests that release rates would vary considerably in the gastro-intestinal tract.

The importance of the true partition coefficient on drug release from both the oily solution and emulsion has been demonstrated by incorporating different drugs in a model emulsion. The results showed that these two parameters are inversely related. This relationship could be useful in formulation studies, for example, an emulsion system could be designed to release the drug either quickly or slowly.

The viscosity of the oil phase could be changed and this might also be used to control the drug release. In order to achieve this, a system has to be designed so that the release should be controlled by the diffusion of the drug in the oil phase. The results reported in Chapter 5 (5.3.7) strongly suggest that, in the case of the oily gels prepared with Aerosil 200 and Aerosil 300, it was the network formed by the interparticle hydrogen-bonding of the silicon dioxide molecules which was responsible for the slow release rather than the increased viscosity. However, it was not intended to include in this study an investigation to determine whether the network formation provides a matrix-controlled rather than a diffusion-controlled release. If the former

is true then these gels would have potential as sustained release systems.

The stability tests reported in Chapter 6 indicated that, except when Span 80 alone or Tween 20-Span 80 mixtures were used to give low HLB values, Miglyol emulsions were stable and consisted of globules mostly smaller than 1 μm in diameter. Since microscopy was used to determine the particle size distribution, the suitability of this method was suspected. Therefore, a second method, photosedimentometry, was used and this showed clearly that microscopy was unsatisfactory for accurate globule size analysis. Microscopy could nonetheless provide information about the gross stability of these emulsions. The stability tests, including the photosedimentometric size distribution analysis, have shown that the emulsions subjected to long term testing were extremely stable even at elevated temperatures. The long term release experiments also supported the results from the stability tests. These emulsions therefore, would be suitable for oral and parenteral use. The long shelf-life, the submicrometer size-range and the narrow size distribution are desirable properties for an emulsion as a drug-delivery system. These emulsions were stable also at the pH range of 2.2 to 8.0 which again indicates the suitability of them for administration by any route.

7.2 Suggestions for further work

(1) Although in-vitro studies provided some explanation about the factors affecting the drug release from these

emulsions, in-vivo experiments can be performed in order to determine any correlation. Lin et al. (1974) have reported good in-vivo correlations of the amount of ephedrine recovered from the urine (0-48 hr) with the total dialyzed in-vitro (0-240 min). The technique they used in the in-vitro experiments was similar to the technique used in these studies (Fincher and Waggoner, 1971). However, poor correlation between the rates of availability and the rates of dialysis at all HLB values were noted. Considering the nature of the systems involved, the correlations of availabilities between in-vivo and in-vitro data was accepted as satisfactory. Therefore it is desirable to determine if similar results would be observed in-vivo.

(2) The effect of silicon dioxide on drug release should be investigated in more detail. If this system provides a matrix-controlled rather than diffusion-controlled release, then these gels could have potential as sustained-release systems even when low concentrations of the gelling agents are present.

(3) As reported in the literature (Higuchi, 1964; Ghanem et al., 1969; Surpuriya et al., 1972a; McNulty, 1975), the particle size of the globules can influence the release rate. However, it has been suggested that when the rate is too low or too high, there is no relationship between the size and the release. In this study due to the extreme stability of the emulsions, the effect of ageing or the size distribution on drug release from the emulsions could not be studied. Therefore, this should be studied by preparing emulsions having different size distributions.

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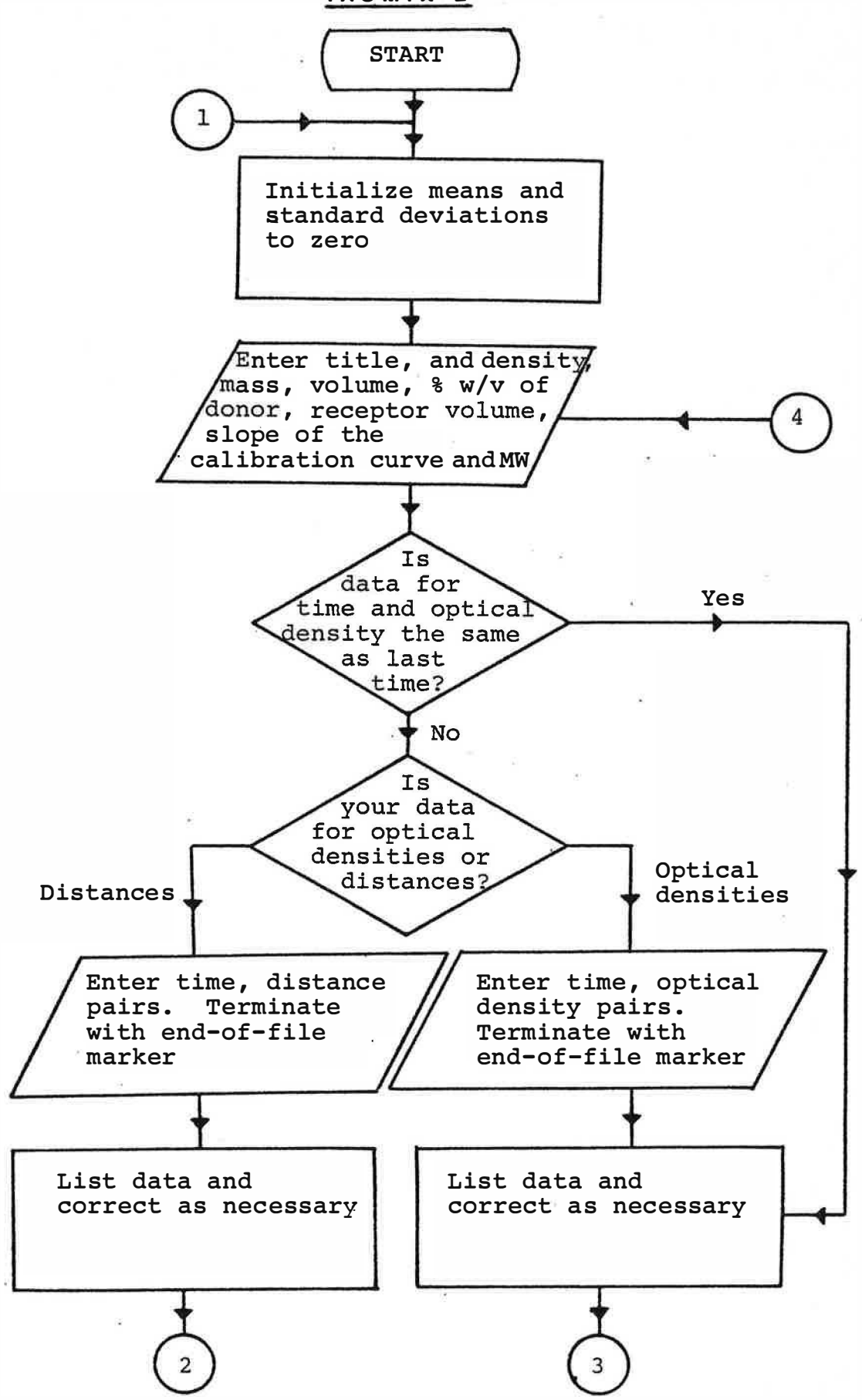
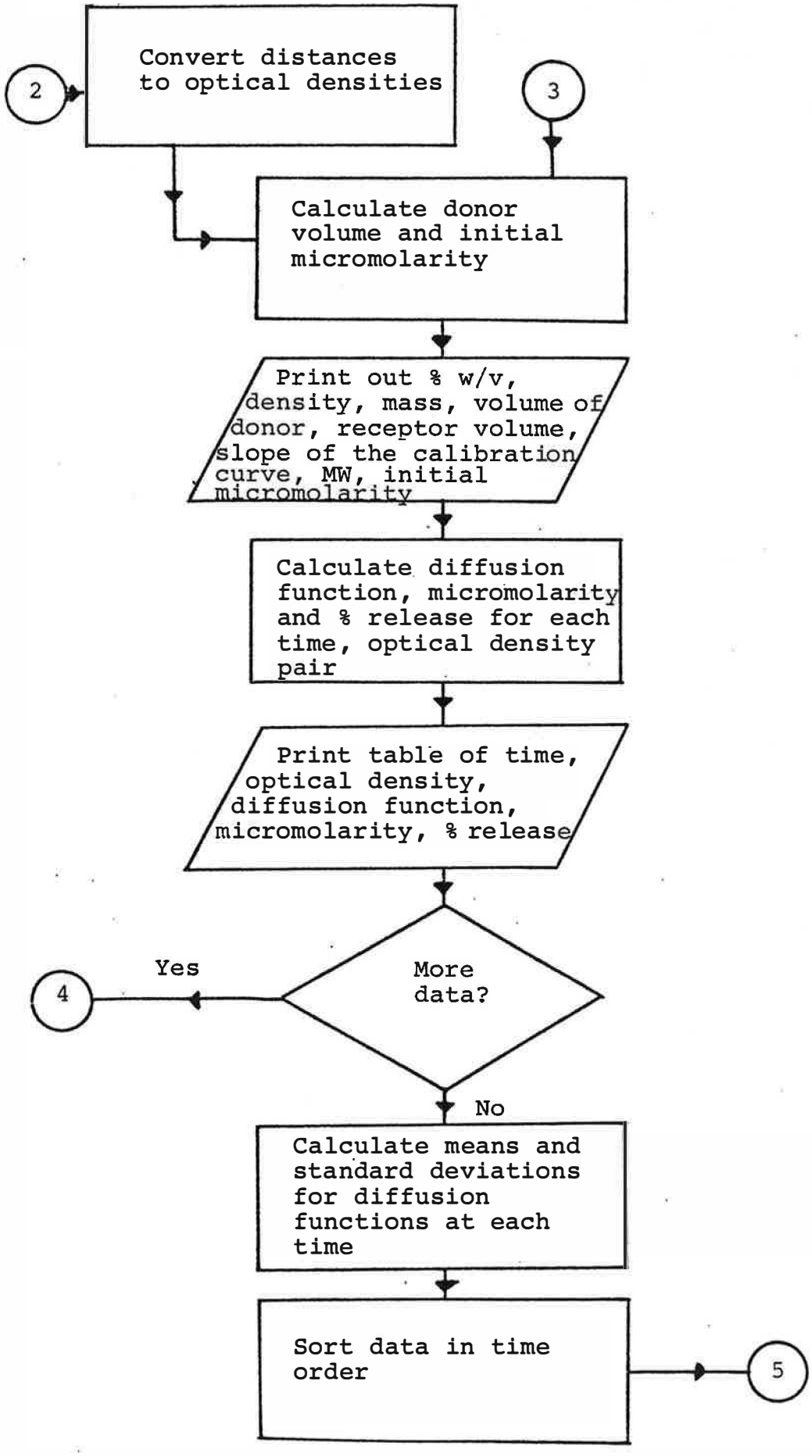
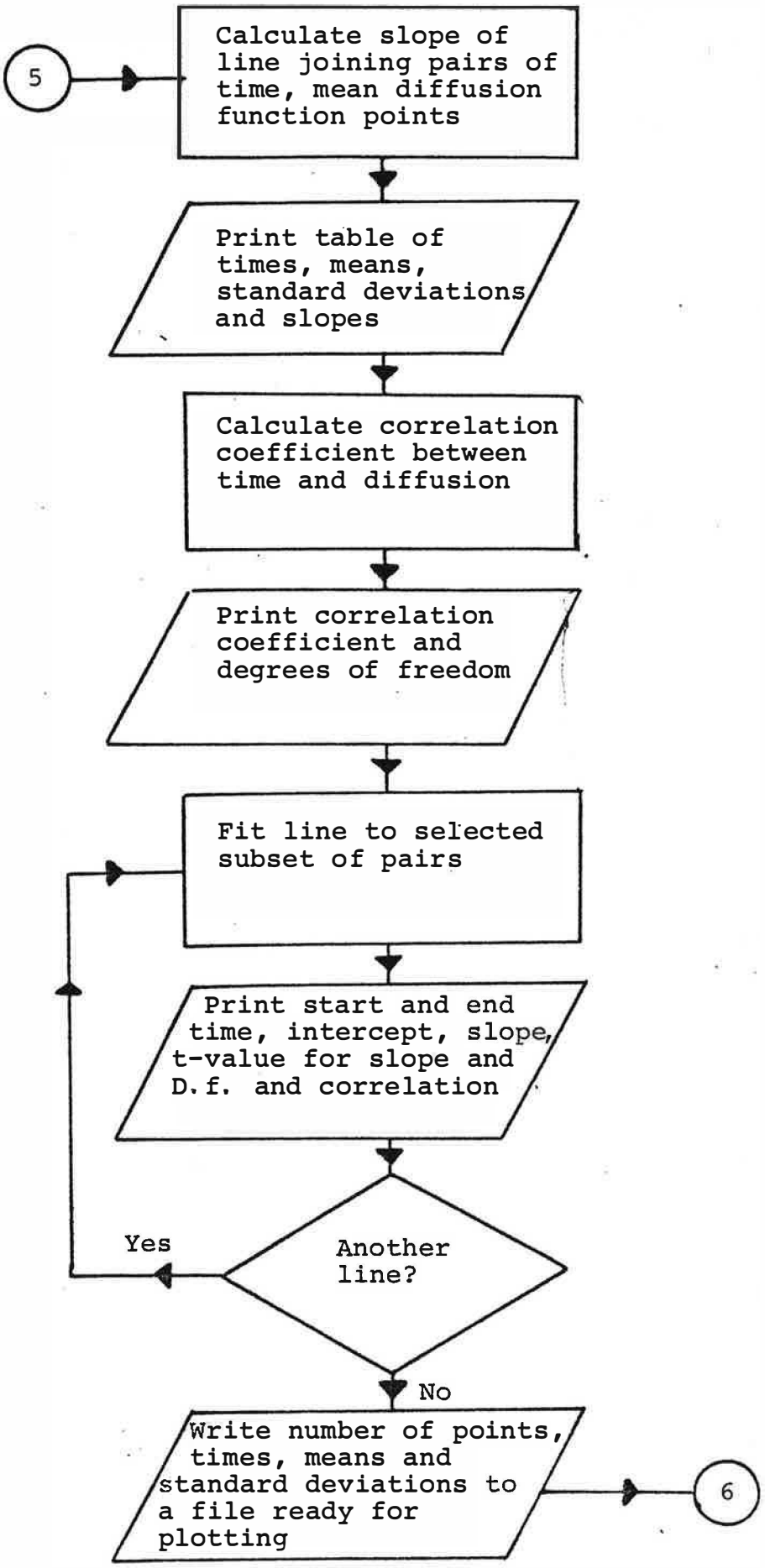
APPENDIX I

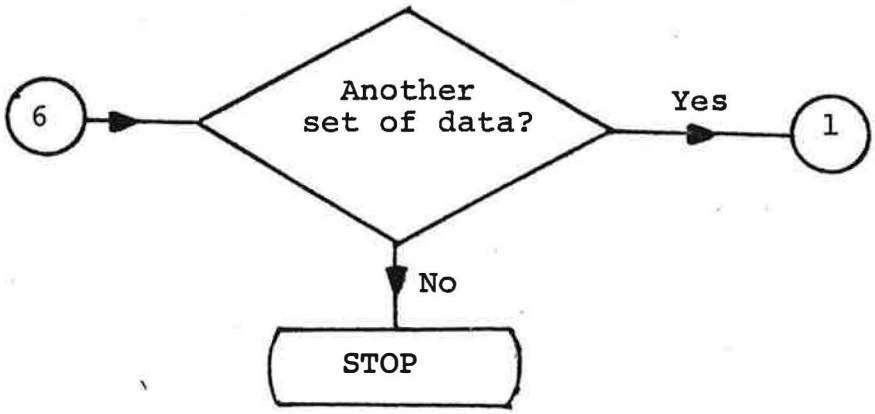
As mentioned in Chapter 3, Diffusion function D(f) was calculated with a computer program which is listed in Figure AI.2. As shown in Figure AI.1 where the flow diagram is drawn, the calculated D(f) values were used to plot the release curves.

Figure AI.1. Flow diagram of the computer program used for calculations and plotting the release curves.

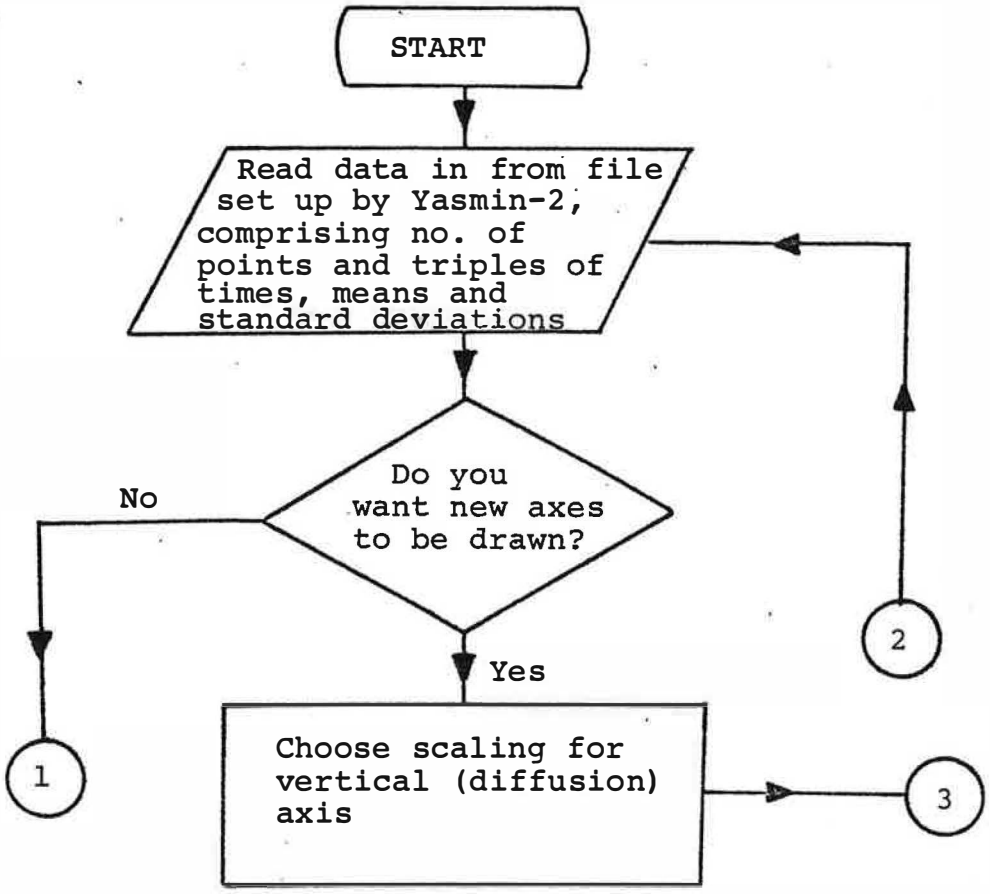



2
Convert distances to optical densities
3
Calculate donor volume and initial micromolarity
Print out % w/v, density, mass, volume of donor, receptor volume, slope of the calibration curve, MW, initial micromolarity
Calculate diffusion function, micromolarity and % release for each time, optical density pair
Print table of time, optical density, diffusion function, micromolarity, % release
More data?
Yes
4
No
Calculate means and standard deviations for diffusion functions at each time
Sort data in time order
5


5
Calculate slope of line joining pairs of time, mean diffusion function points
Print table of times, means, standard deviations and slopes
Calculate correlation coefficient between time and diffusion
Print correlation coefficient and degrees of freedom
Fit line to selected subset of pairs
Print start and end time, intercept, slope, t-value for slope and D.f. and correlation
Another line?
Yes
No
Write number of points, times, means and standard deviations to a file ready for plotting
6


6
Another set of data?
Yes
1
No
STOP

GRAPH


START
Read data in from file set up by Yasmin-2, comprising no. of points and triples of times, means and standard deviations
Do you want new axes to be drawn?
No
Yes
2
1
Choose scaling for vertical (diffusion) axis
3

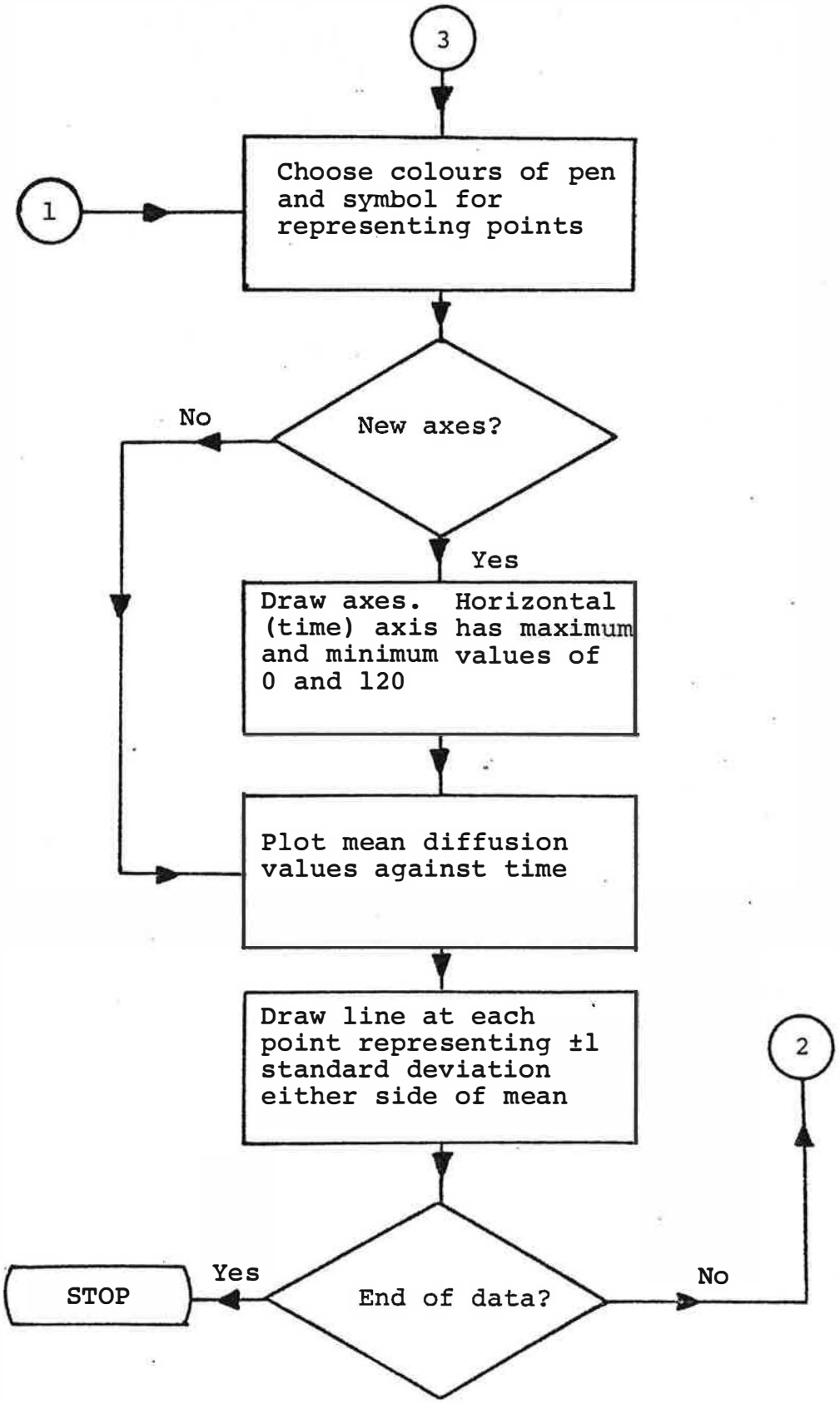

3
1
Choose colours of pen and symbol for representing points
New axes?
No
Yes
Draw axes. Horizontal (time) axis has maximum and minimum values of 0 and 120
Plot mean diffusion values against time
Draw line at each point representing ±1 standard deviation either side of mean
2
End of data?
Yes
No
STOP

Figure AI.2. Listing of the computer program.

YASMIN-2

```
      DIMENSION TITLE(26),R1S(100),R2S(100),R5S(100),R6S(100),PER(100)
      DIMENSION NO(100),SLOPE(100),SS(100),DATA(100),TIME(100)
      DIMENSION RNGE(4)
      REAL MEAN(100),SD(100)
      DATA RNGE/0.2,0.5,1.0,2.0/
   34 ND=0
      DO 100 I=1,100
      MEAN(I)=0.0
      NO(I)=0
  100 SS(I)=0.0
   20 WRITE(12,11)
  117 READ(11,12,END=22)IA
      IF(IA.EQ.'Y')GO TO 22
      IF(IA.NE.'N')GO TO 117
      WRITE(12,14)
      READ(11,15,END=22)TITLE
      WRITE(13,16)TITLE
      WRITE(12,1)
      READ(11,-,END=22)DATA(1)
      WRITE(12,3)
      READ(11,-)DATA(2)
      WRITE(12,4)
      READ(11,-)DATA(3)
      WRITE(12,5)
      READ(11,-)DATA(4)
      WRITE(12,17)
      READ(11,-)DATA(5)
      WRITE(12,18)
      READ(11,-)DATA(6)
  118 WRITE(12,51)
      READ(11,12)IA
      IF(IA.EQ.'Y')GO TO 52
      IF(IA.NE.'N')GO TO 118
  116 WRITE(12,55)
      READ(11,12)IA
      IF(IA.EQ.'O')IFLAG=0
      IF(IA.EQ.'D')IFLAG=1
      IF(IA.NE.'O'.AND.IA.NE.'D')GO TO 116
      M=6
   21 WRITE(12,8)
      M=M+1
      READ(11,-,END=23)DATA(M)
      M=M+1
      IF(IFLAG.EQ.0)THEN
      WRITE(12,56)
      ELSE
      WRITE(12,9)
      ENDIF
      READ(11,-)DATA(M)
      GOTO 21
   23 M=M-1
   52 WRITE(12,48)
      WRITE(12,35)DATA(1)
      WRITE(12,36)DATA(2)
      WRITE(12,37)DATA(3)
      WRITE(12,38)DATA(4)
      WRITE(12,39)DATA(5)
      WRITE(12,54)DATA(6)
      DO 107 I=7,M,2
      I1=I+1
```

```
      WRITE(12,40)I,DATA(I)
      WRITE(12,41)I1,DATA(I1)
  107 CONTINUE
   46 WRITE(12,42)
      READ(11,12)IA
      IF(IA.EQ.'N')GO TO 43
      IF(IA.NE.'Y')GO TO 46
      WRITE(12,44)
      READ(11,-)I
      WRITE(12,45)
      READ(11,-)DATA(I)
      GO TO 46
   43 A=DATA(1)
      B=DATA(2)
      C=DATA(3)
      Y=DATA(4)
      D=DATA(5)
      WM=DATA(6)
      N=0
      J=1
      DO 108 I=7,M,2
      I1=I+1
      IM1=I-1
      N=N+1
      R1S(N)=DATA(I)
      IF(IFLAG.EQ.0)THEN
      R2S(N)=DATA(I1)
      ELSE
      IF(I.GT.7.AND.DATA(I1).LT.DATA(IM1))J=J+1
      IF(J.GT.4)THEN
      WRITE(3,53)
      GO TO 52
      ENDIF
      R2S(N)=DATA(I1)*RNGE(J)/250
      ENDIF
  108 CONTINUE
      X=C/B
      R0=(X*Y)/(X+Y)
      R3=A/WM*1E7
      R4=1+Y/X
      WRITE(12,6)A,B,C,X,Y,D,WM
      WRITE(13,6)A,B,C,X,Y,D,WM
      WRITE(13,2)R3
      WRITE(13,7)
      DO 25 I=1,N
      R6S(I)=R2S(I)*D/WM*1E7
      R5S(I)=R0*ALOG(R3/(R3-R6S(I)*R4))
      PER(I)=R2S(I)*100*D*Y/(A/B)/C
      WRITE(13,10)R1S(I),R2S(I),R5S(I),R6S(I),PER(I)
   25 CONTINUE
      WRITE(13,13)
      DO 110 I=1,N
      DO 111 J=1,ND
      IF(R1S(I).NE.TIME(J))GO TO 111
      NO(J)=NO(J)+1
      MEAN(J)=MEAN(J)+R5S(I)
      SS(J)=SS(J)+R5S(I)**2
      GO TO 110
  111 CONTINUE
      ND=ND+1
```

```
      NO(ND)=NO(ND)+1
      MEAN(ND)=MEAN(ND)+R5S(I)
      SS(ND)=SS(ND)+R5S(I)**2
      TIME(ND)=R1S(I)
  110 CONTINUE
      GOTO 20
   22 WRITE(13,13)
      DO 101 I=1,ND
      MEAN(I)=MEAN(I)/NO(I)
      SD(I)=SS(I)-NO(I)*MEAN(I)**2
      IF(SD(I).GT.0.0.AND.NO(I).GT.1)SD(I)=SQRT(SD(I)/(NO(I)-1))
  101 CONTINUE
      ND1=ND-1
  112 IFLAG=0
      DO 113 I=1,ND1
      IF(TIME(I).LE.TIME(I+1))GO TO 113
      X=TIME(I)
      Y=MEAN(I)
      Z=SD(I)
      W=SS(I)
      M=NO(I)
      TIME(I)=TIME(I+1)
      MEAN(I)=MEAN(I+1)
      SD(I)=SD(I+1)
      SS(I)=SS(I+1)
      NO(I)=NO(I+1)
      TIME(I+1)=X
      MEAN(I+1)=Y
      SD(I+1)=Z
      SS(I+1)=W
      NO(I+1)=M
      IFLAG=1
  113 CONTINUE
      IF(IFLAG.EQ.1)GO TO 112
      DO 103 I=1,ND1
      SLOPE(I+1)=(MEAN(I+1)-MEAN(I))/(TIME(I+1)-TIME(I))
  103 CONTINUE
      WRITE(12,26)
      WRITE(13,26)
      WRITE(12,27)TIME(1),MEAN(1),SD(1)
      WRITE(13,27)TIME(1),MEAN(1),SD(1)
      DO 104 I=2,ND
      WRITE(12,27)TIME(I),MEAN(I),SD(I),SLOPE(I)
      WRITE(13,27)TIME(I),MEAN(I),SD(I),SLOPE(I)
  104 CONTINUE
      N=0
      XY=0
      X2=0
      XM=0
      YM=0
      Y2=0
      DO 109 I=1,ND
      N=N+NO(I)
      XY=XY+NO(I)*TIME(I)*MEAN(I)
      XM=XM+NO(I)*TIME(I)
      YM=YM+NO(I)*MEAN(I)
      X2=X2+NO(I)*TIME(I)**2
      Y2=Y2+SS(I)
  109 CONTINUE
      XM=XM/N
```

```
      YM=YM/N
      B2=XY-N*XM*YM
      B3=X2-N*XM**2
      B4=Y2-N*YM**2
      IF(B3.EQ.0.0.OR.B4.EQ.0.0)GO TO 114
      R=B2/SQRT(B3*B4)
      N2=N-2
      WRITE(12,47)R,N2
      WRITE(13,47)R,N2
  114 WRITE(12,28)
      READ(11,-)T0
      WRITE(12,29)
      READ(11,-)T1
      DO 105 I=1,ND
      IF(TIME(I).EQ.T0)J0=I
      IF(TIME(I).EQ.T1)J1=I
  105 CONTINUE
      IF(J0.LT.1.OR.J0.GT.ND)J0=1
      IF(J1.LT.1.OR.J1.GT.ND)J1=ND
      N=0
      XY=0
      X2=0
      XM=0
      YM=0
      Y2=0
      DO 106 I=J0,J1
      N=N+NO(I)
      XY=XY+NO(I)*TIME(I)*MEAN(I)
      XM=XM+NO(I)*TIME(I)
      YM=YM+NO(I)*MEAN(I)
      X2=X2+NO(I)*TIME(I)**2
      Y2=Y2+SS(I)
  106 CONTINUE
      XM=XM/N
      YM=YM/N
      B2=XY-N*XM*YM
      B3=X2-N*XM**2
      IF(B3.EQ.0.0)GO TO 115
      B1=B2/B3
      B0=YM-B1*XM
      B4=Y2-N*YM**2
      S=B4-B2**2/B3
      S=S/(N-2)
      S=SQRT(S/B3)
      T=B1/S
      N2=N-2
      IF(B4.EQ.0.0)GO TO 115
      R=B2/SQRT(B3*B4)
      WRITE(12,30)T0,T1,B0,B1,T,N2,R
      WRITE(13,30)T0,T1,B0,B1,T,N2,R
  115 WRITE(12,50)
      READ(11,12)IA
      IF(IA.EQ.'Y')GO TO 114
      IF(IA.NE.'N')GO TO 115
      WRITE(13,13)
      WRITE(14,200)ND
      WRITE(14,201)(TIME(I),MEAN(I),SD(I),I=1,ND)
  119 WRITE(12,33)
      READ(11,12)IA
      IF(IA.EQ.'Y')GO TO 34
```

```
      IF(IA.NE.'N')GO TO 119
      STOP
    1 FORMAT(' GIVE DONOR %W/VOL')
    2 FORMAT(21X,'INITIAL C1 =',F10.2,'  MICROMOLAR'//21X,
     C'--------------------------------'//)
    3 FORMAT(' GIVE DONOR DENSITY')
    4 FORMAT(' GIVE DONOR MASS')
    5 FORMAT(' GIVE RECEPTOR VOLUME')
    6 FORMAT(21X,'DONOR %W/VOL',F13.4/
     C21X,'DONOR DENSITY',F12.4,'  G/CC'/21X,'DONOR MASS',
     CF15.4,'  G'/21X,'DONOR VOLUME',F13.4,'  CC'/
     C21X,'RECEPTOR VOLUME',F10.4,'  CC'//21X,
     C'SLOPE OF CALIBRATION CURVE',F15.8//21X,
     C'MOLECULAR WEIGHT',F21.4,'  G'//21X,
     C'--------------------------------'/)
    8 FORMAT(' GIVE TIME')
    7 FORMAT(21X,'TIME  OPTICAL  DIFFUSION       C2 MICROMOLARITY  PERCE
     CNT'/27X,'DENSITY  FUNCTION                        RELEASE'/)
    9 FORMAT(' GIVE DISTANCE')
   10 FORMAT(F25.2,F8.3,F12.4,F19.4,F12.3)
   11 FORMAT(' HAVE YOU FINISHED (Y/N) ?')
   13 FORMAT(15(/))
   14 FORMAT('  GIVE TITLE')
   17 FORMAT(' GIVE SLOPE OF CALIBRATION CURVE')
   18 FORMAT(' GIVE MOLECULAR WEIGHT(G)')
   12 FORMAT(A1)
   16 FORMAT(5X,26A3///)
   15 FORMAT(26A3)
   26 FORMAT(35X,'DIFFUSION   FUNCTION'/21X,'TIME',6X,'MEAN',8X,
     C'SD',10X,'SLOPE')
   27 FORMAT(F25.2,3F12.4)
   28 FORMAT(' GIVE TIME FOR START OF LINE TO BE FITTED')
   29 FORMAT(' GIVE TIME FOR END OF LINE TO BE FITTED')
   30 FORMAT(///'  THE FITTED LINE BETWEEN TIMES',F7.2,' AND',F7.2,
     C' ,HAS'/13X,'INTERCEPT',F12.4/17X,'SLOPE',F12.4/5X,
     C'T-VALUE FOR SLOPE',F12.4/4X,'DEGREES OF FREEDOM',I8/
     C5X,'CORRELATION COEF.',F12.4)
   33 FORMAT(' DO YOU HAVE ANOTHER SET OF DATA (Y/N) ?')
   48 FORMAT(' THIS IS THE DATA YOU HAVE JUST ENTERED:')
   35 FORMAT('  1  DONOR %W/VOL',14X,F13.8)
   36 FORMAT('  2  DONOR DENSITY',13X,F13.8)
   37 FORMAT('  3  DONOR MASS',16X,F13.8)
   38 FORMAT('  4  RECEPTOR VOLUME',11X,F13.8)
   39 FORMAT('  5  SLOPE OF CALIBRATION CURVE',F13.8)
   40 FORMAT(1X,I2,'  TIME',22X,F13.8)
   41 FORMAT(1X,I2,'  DISTANCE',18X,F13.8)
   42 FORMAT(' DO YOU WANT TO MAKE A CORRECTION (Y/N) ?')
   44 FORMAT(' GIVE THE DATA LINE NUMBER')
   45 FORMAT(' GIVE THE CORRECT DATA VALUE')
   47 FORMAT(/20X,'CORRELATION COEFFICIENT',F12.4/
     C25X,'DEGREES OF FREEDOM',I8)
   50 FORMAT(' DO YOU WANT TO FIT ANOTHER LINE (Y/N) ?')
   51 FORMAT(' IS THE DATA FOR TIME AND OPTICAL DENSITY ',
     *'THE SAME AS LAST TIME (Y/N) ?')
   53 FORMAT(' ***SOMETHING WRONG WITH DISTANCES!'/)
   54 FORMAT('  6  MOLECULAR WEIGHT',10X,F13.8)
   55 FORMAT(' DO YOU HAVE OPTICAL DENSITIES OR DISTANCES (O/D) ?')
   56 FORMAT(' GIVE OPTICAL DENSITY')
  200 FORMAT(I3)
  201 FORMAT(3F12.4)
      END
```

GRAPH

```
      REAL TIME(100),MEAN(100),SD(100)
      LOOP
      READ(14,-,END=999)ND
      READ(14,-)(TIME(I),MEAN(I),SD(I),I=1,ND)
      WRITE(12,31)
      READ(11,12)I
      IF(I.NE.'NO'.AND.I.NE.'N')THEN
      WRITE(12,33)
      READ(11,-)YMAX
      ENDIF
      WRITE(12,49)
      READ(11,-)NPEN
      WRITE(12,51)
      READ(11,-)NSYM
      CALL HP7220
      CALL CHASIZ(2.5,2.5)
      CALL WINDOW(2)
      CALL PENSEL(NPEN,0.0,0)
      CALL AXIPOS(0,15.0,15.0,150.0,1)
      CALL AXIPOS(0,15.0,15.0,240.0,2)
      CALL AXISCA(1,10,0.0,120.0,1)
      CALL AXISCA(1,10,0.0,YMAX,2)
      IF(I.EQ.'NO')GO TO 32
      IF(I.EQ.'N')GO TO 32
      CALL PICCLE
      CALL AXIDRA(-2,1,1)
      CALL MOVTO2(155.0,20.0)
      CALL CHAHOL('TIME*.')
      CALL AXIDRA(2,-1,2)
      CALL MOVTO2(0.0,250.0)
      CALL CHAHOL('P(F)*.')
   32 CALL GRASYM(TIME,MEAN,ND,NSYM,0)
      DO 102 I=1,ND
      ST=MEAN(I)+SD(I)
      FIN=MEAN(I)-SD(I)
      CALL GRAMOV(TIME(I),ST)
      CALL GRALIN(TIME(I),FIN)
  102 CONTINUE
      CALL DEVEND
      ENDLOOP
  999 STOP
   12 FORMAT(A3)
   31 FORMAT(' DO YOU WANT TO DRAW NEW AXES?')
   49 FORMAT(' GIVE NUMBER OF PEN TO BE USED')
   51 FORMAT(' GIVE NUMBER OF SYMBOL REQUIRED')
   33 FORMAT(' GIVE MAXIMUM VALUE FOR VERTICAL AXIS(E.G. 6.0,1.5,ETC)')
      END
```

APPENDIX II

The equation of the calibration line for each drug using three spectrophotometers was calculated with a computer program. Table AII.1 shows the equations of the lines for the drugs used together with the correlation coefficients and the degrees of freedoms. The solutions were prepared in distilled water and λ_{max} (nm) values correspond to the maximum wavelength of absorption in water. Table AII.2 shows the equations of the lines obtained for salicylic acid in McIlvane buffer solutions at λ_{max} = 297 nm.

Table AII.1. Equations of calibration lines obtained for the drugs studied. Test solutions are prepared in distilled water.

Drug	λ_{max} (nm)	Equation of the regression line as $C(g.l^{-1})$ = O.D. x slope, correlation coefficient; degress of freedom		
		Cecil 212	Cecil 272	Perkin-Elmer
Benzoic acid	227	$C = O.D.x1.3526x10^{-2}$, 0.9997; 5	$C = O.D.x1.3189x10^{-2}$, 0.9998; 5	$C = O.D.x1.2844x10^{-2}$, 0.9999; 5
3-Hydroxy benzoic acid	288	$C = O.D.x6.6832x10^{-2}$, 0.9996; 10	$C = O.D.x6.6382x10^{-2}$, o.9999; 10	$C = O.D.x6.6002x10^{-2}$, 0.9993; 10
Salicylic acid	297	$C = O.D.x4.1581x10^{-2}$, o.9998; 7	$C = O.D.x4.0503x10^{-2}$, o.9998; 7	$C = O.D.x3.9818x10^{-2}$, 1.000; 7
Aspirin	297	$C = O.D.x2.2125x10^{-1}$, 0.9992; 5	$C = O.D.x2.1593x10^{-1}$, 0.9984; 5	$C = O.D.x2.1737x10^{-1}$, 0.9989; 17
Paracetamol	243	$C = O.D.x1.6019x10^{-2}$, 0.9989; 5	$C = O.D.x1.5308x10^{-2}$, 0.9999; 5	$C = O.D.x1.5215x10^{-2}$, 0.9999; 7
Phenacetin	245	$C = O.D.x1.6208x10^{-2}$, 0.9998; 4	$C = O.D.x1.6469x10^{-2}$, o.9998; 4	$C = O.D.x1.5879x10^{-2}$, 0.9999; 4

Table AII.2. Equations of the calibration lines for salicylic acid in McIlvane buffer solutions at λ_{max} = 297 nm.

pH of the buffer solution	Equation of the line as $C(g.l^{-1})$ = O.D. x slope, correlation coefficient; degrees of freedom	
	Cecil 212	Cecil 272
2.2	$C = O.D. \times 4.1143 \times 10^{-2}$, 0.9996; 8	$C = O.D. \times 4.0201 \times 10^{-2}$, 0.9998; 7
3.0	$C = O.D. \times 4.1547 \times 10^{-2}$, 0.9997; 6	$C = O.D. \times 4.0443 \times 10^{-2}$, 0.9998; 4
5.0	$C = O.D. \times 3.8654 \times 10^{-2}$, 0.9998; 8	$C = O.D. \times 3.9765 \times 10^{-2}$, 0.9999; 8
7.0	$C = O.D. \times 3.9217 \times 10^{-2}$, 0.9996; 5	$C = O.D. \times 3.8629 \times 10^{-2}$, 0.9994; 5

APPENDIX III

In this appendix the statistical analysis between the parameters used to plot the graphs given in Figures 5.9, 5.10, 5.12, 5.13 and 5.14 are presented. The equations of the regression lines fitted for each case and the common line which can be fitted to represent these separate lines were calculated with the overall correlation coefficient, r. The F values were calculated from the ratio of the variances estimated by eq. (AIII.1) and (AIII.2) where V_1 and V_2 are the degrees of freedoms.

Sums of squares:

$$\frac{[\Sigma\ (X-\bar{X}_1)(Y-\bar{Y}_1)]^2}{\Sigma\ (X-\bar{X}_1)^2} + \ldots. \quad - \quad \frac{[\Sigma\ (X-\bar{X}_1)(Y-\bar{Y}_1) + \ldots.]^2}{\Sigma\ (X-\bar{X}_1)^2 + \ldots.} \qquad \text{(AIII.1)}$$

$V_1 = u-1$ (u is the number of the individual lines).

Sum of sums of squares:

$$\sum_{1}^{u} \Sigma\ (Y-\bar{Y}_1)^2 - \frac{[\Sigma\ (X-\bar{X}_1)(Y-\bar{Y}_1)]^2}{\Sigma\ (X-\bar{X}_1)^2} \qquad \text{(AIII.2)}$$

$V_2 = N_1 + N_2 + \ldots. - 2u.$

The results of the calculations are summarized in Tables AIII.1 to AIII.5.

Table AIII.1. Summary of the statistical analysis data for Figure 5.9.

Line fitted for	Equation of the regression line
Emulsion II-1, II-2, II-3	$Y_1 = -18.85 \times 10^{-4} + 0.6091X_1$
Emulsion II-4, II-5, II-6	$Y_2 = -28.45 \times 10^{-4} + 0.6980X_2$
Emulsion II-7, II-8, II-9	$Y_3 = -22.82 \times 10^{-4} + 0.7477X_3$
Common line and the	$Y = -15.05 \times 10^{-4} + 0.6228X$
correlation coefficient	$r = 0.9643$

F value for	F	V_1	V_2
Slopes	0.9521	2.0	3.0
Intercepts	7.2530	2.0	5.0

Table AIII.2. Summary of the statisticsl analysis data for Figure 5.10.

Line fitted for	Equation of the regression line
Emulsion II-1, II-2, II-3	$Y_1 = 24.81 \times 10^{-4} + 0.5140X_1$
Emulsion II-4, II-5, II-6	$Y_2 = 20.69 \times 10^{-4} + 0.5707X_2$
Emulsion II-7, II-8, II-9	$Y_3 = 24.76 \times 10^{-4} + 0.5857X_3$
Common line and the	$Y = 24.69 \times 10^{-4} + 0.5407X$
correlation coefficient	$r = 0.9901$

F value for	F	V_1	V_2
Slopes	0.7534	2.0	3.0
Intercepts	2.6150	2.0	5.0

Table AIII.3. Summary of the statistical analysis data for Figure 5.12.

Line fitted for	Equation of the regression line
ϕ = 20/80	$Y_1 = 81.96 \times 10^{-4} + 0.4436 \times 10^{-4} X_1$
ϕ = 40/60	$Y_2 = 59.69 \times 10^{-4} + 0.1355 \times 10^{-4} X_2$
ϕ = 60/40	$Y_3 = 48.06 \times 10^{-4} - 0.4370 \times 10^{-5} X_3$
Common line and the	$Y = 184.4 \times 10^{-4} - 0.1435 \times 10^{-4} X$
correlation coefficient	r = -0.6370

F value for	F	V_1	V_2
Slopes	11.19	2.0	3.0
Intercepts	325.7	2.0	5.0

Table AIII.4. Summary of the statistical analysis data for Figure 5.13.

Line fitted for	Equation of the regression line
ϕ = 20/80	$Y_1 = 98.90 \times 10^{-4} + 0.1414 \times 10^{-3} X_1$
ϕ = 40/60	$Y_2 = 67.37 \times 10^{-4} + 0.4592 \times 10^{-4} X_2$
ϕ = 60/40	$Y_3 = 44.45 \times 10^{-4} + 0.2400 \times 10^{-5} X_3$
Common line and the	$Y = 43.90 \times 10^{-4} + 0.4788 \times 10^{-3} X$
correlation coefficient	r = 0.5374

F value for	F	V_1	V_2
Slopes	5.933	2.0	3.0
Intercepts	401.8	2.0	5.0

Table AIII.5. Summary of the statistical analysis data for Figure 5.14.

Line fitted for	Equation of the regression line
Emulsion II-1, II-2, II-3	$Y_1 = 119.5 \times 10^{-4} - 0.5246 \times 10^{-2} X_1$
Emulsion II-4, II-5, II-6	$Y_2 = 117.5 \times 10^{-4} - 0.5246 \times 10^{-2} X_2$
Emulsion II-7, II-8, II-9	$Y_3 = 108.4 \times 10^{-4} - 0.4444 \times 10^{-2} X_3$
Common line and the correlation coefficient	$Y = 115.1 \times 10^{-4} - 0.4979 \times 10^{-2} X$ $r = 0.9438$

F value for	F	V_1	V_2
Slopes	0.0778	2.0	3.0
Intercepts	0.1163	2.0	5.0

APPENDIX IV

Particle size distribution on various bases were calculated with a computer program as mentioned in Chapter 6. Table AIV.1 shows a typical output obtained for Emulsion II-1 by photosedimentometry.

Table AIV.1. Typical output of the computer program used for sedimentometric analysis.

PARTICLE SIZE DISTRIBUTION FROM PHOTOFUGE DATA

D	I	VOLUME BASE (V)	VOLUME BASE (SUM)	VOLUME BASE (O/O)	SURFACE AREA BASE (A)	SURFACE AREA BASE (SUM)	SURFACE AREA BASE (O/O)	LENGTH BASE (L)	LENGTH BASE (SUM)	LENGTH BASE (O/O)	NUMBER BASE (N)	NUMBER BASE (SUM)	NUMBER BASE (O/O)
.150	3.170												
.175		21.808	21.808	55.305	124.615	124.615	65.301	712.088	712.088	73.104	4069.074	4069.074	79.195
.200	3.960												
.225		8.901	30.709	77.879	39.560	164.176	86.032	175.824	887.912	91.154	781.441	4850.515	94.404
.250	4.700												
.275		4.231	34.940	88.608	15.385	179.560	94.094	55.944	943.856	96.897	203.433	5053.947	98.364
.300	5.200												
.325		1.829	36.768	93.246	5.627	185.187	97.042	17.314	961.170	98.674	53.273	5107.221	99.400
.350	5.550												
.375		.974	37.742	95.715	2.596	187.784	98.403	6.923	968.093	99.385	18.462	5125.682	99.760
.400	5.820												
.425		.500	38.242	96.983	1.176	188.960	99.019	2.768	970.861	99.669	6.513	5132.196	99.887
.450	6.000												
.475		.291	38.533	97.722	.613	189.573	99.341	1.291	972.152	99.802	2.718	5134.914	99.939
.500	6.130												
.550		.336	38.869	98.574	.611	190.184	99.661	1.111	973.263	99.916	2.020	5136.933	99.979
.600	6.320												
.650		.161	39.030	98.981	.247	190.431	99.790	.380	973.643	99.955	.586	5137.518	99.990
.700	6.430												
.750		.107	39.137	99.253	.143	190.574	99.865	.190	973.834	99.975	.254	5137.772	99.995
.800	6.510												
.850		.076	39.213	99.447	.090	190.664	99.912	.106	973.939	99.985	.124	5137.897	99.998
.900	6.570												
.950		.049	39.262	99.571	.051	190.715	99.939	.054	973.994	99.991	.057	5137.954	99.999
1.000	6.610												
1.100		.060	39.322	99.723	.055	190.770	99.968	.050	974.043	99.996	.045	5137.999	99.999
1.200	6.660												
1.300		.036	39.359	99.815	.028	190.798	99.982	.022	974.065	99.998	.017	5138.015	100.000
1.400	6.699												
1.500		.012	39.371	99.847	.008	190.806	99.987	.006	974.070	99.999	.004	5138.019	100.000
1.600	6.700												
1.700		.013	39.384	99.879	.008	190.814	99.991	.004	974.075	99.999	.003	5138.022	100.000
1.800	6.710												
1.900		.013	39.397	99.913	.007	190.821	99.994	.004	974.078	100.000	.002	5138.024	100.000
2.000	6.720												
2.250		0	39.397	99.913	0	190.821	99.994	0	974.078	100.000	0	5138.024	100.000
2.500	6.720												
2.750		.015	39.413	99.952	.006	190.827	99.997	.002	974.080	100.000	.001	5138.024	100.000
3.000	6.730												
3.250		0	39.413	99.952	0	190.827	99.997	0	974.080	100.000	0	5138.024	100.000
3.500	6.730												
3.750		.019	39.432	100.000	.005	190.832	100.000	.001	974.082	100.000	.000	5138.025	100.000
4.000	6.740												
4.250		0	39.432	100.000	0	190.832	100.000	0	974.082	100.000	0	5138.025	100.000
4.500	6.740												
4.750		0	39.432	100.000	0	190.832	100.000	0	974.082	100.000	0	5138.025	100.000
5.000	6.740												
5.500		0	39.432	100.000	0	190.832	100.000	0	974.082	100.000	0	5138.025	100.000

Table AIV.1. Cont.

D	VOLUME BASE	SURFACE AREA BASE	LENGTH BASE	NUMBER BASE
.150				
.175	55.305	65.301	73.104	79.195
.200				
.225	22.574	20.731	18.050	15.209
.250				
.275	10.729	8.062	5.743	3.959
.300				
.325	4.638	2.949	1.777	1.037
.350				
.375	2.469	1.360	.711	.389
.400				
.425	1.268	.616	.284	.127
.450				
.475	.739	.321	.133	.053
.500				
.550	.852	.320	.114	.039
.600				
.650	.407	.130	.039	.011
.700				
.750	.272	.075	.020	.005
.600				
.850	.194	.047	.011	.002
.900				
.950	.124	.027	.006	.001
1.000				
1.100	.152	.029	.005	.001
1.200				
1.300	.092	.015	.002	.000
1.400				
1.500	.031	.004	.001	.000
1.600				
1.700	.033	.004	.000	.000
1.800				
1.900	.034	.004	.000	.000
2.000				
2.250	0	0	0	0
2.500				
2.750	.039	.003	.000	.000
3.000				
3.250	0	0	0	0
3.500				
3.750	.048	.003	.000	.000
4.000				
4.250	0	0	0	0
4.500				
4.750	0	0	0	0
5.000				
5.500	0	0	0	0

MEAN VOLUME DIAMETER OF PARTICLES IN MEASURED RANGE = .197 MICRONS

RHEOLOGICAL VOLUME DIAMETER OF PARTI CLES IN MEASURED RANGE = .183 MICRONS

VOLUME-SURFACE DIAMETER OF PARTICLES IN MEASURED RANGE = .207 MICRONS

SPECIFIC INTERFACIAL AREA = 20,326 SQ.METERS/C.C.