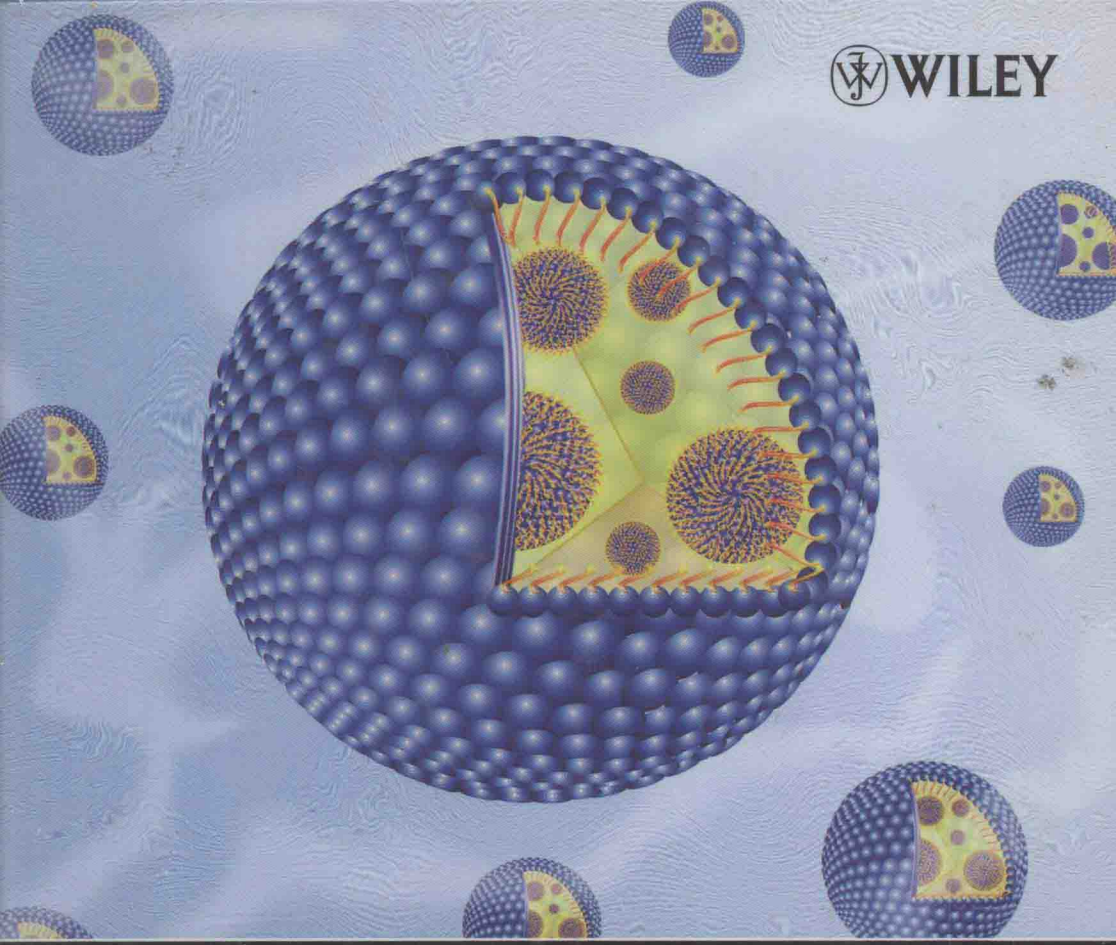
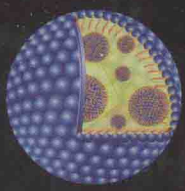


MULTIPLE EMULSIONS

Technology and Applications



EDITED BY

ABRAHAM ASERIN

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TECHNOLOGY AND APPLICATIONS

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MULTIPLE EMULSIONS

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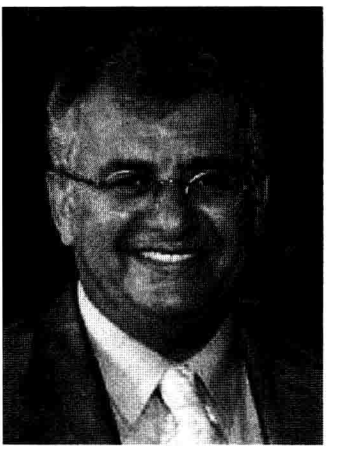
PREFACE

In Honor of Prof. Nissim Garti's 60th Birthday



In 2006, Prof. Nissim Garti celebrated his sixtieth birthday. By that time he had had a brilliant scientific career spanning more than thirty-five years. No happier way can be found of celebrating a scientist's birthday than by issuing a *Festschrift* in his honor. Such a *Festschrift*—be it a special issue of a journal or a book—generally contains studies that intend to reflect various topics relating to the putative extensive work and all-round interests of the honoree. Usually only one *Festschrift* is issued on a particular anniversary. Nissim has justly been awarded two *Festschrifts*!

The first was a special issue of a scientific journal.[1] The intervening year before the publication of the present book has served only to enhance the renown of this outstanding scientist and to increase the fervor and esteem with which this tribute is offered.

Between the covers of this book are published articles written by colleagues, alumni, and friends in honor of Prof. Garti. They are all one in their affection and esteem for his personality and achievements. Many more would have contributed but for space and schedules. Yet all join us in congratulating Prof. Garti on passing his sixtieth birthday and on amassing a lifetime of work

and ground-breaking benchmark accomplishments as one of the most original and innovative scientists in the field of surfactant chemistry.

Whereas the literature cited at the end of this Preface demonstrates ramified and diverse research areas—almost every one of which has long interested Prof. Garti—the present book is focused on one subject: multiple emulsions. This topical choice for the *Festschrift* reflects a challenging area to which Nissim has devoted his talent and efforts over the past two decades, an area in which he pioneered creative ideas and spearheaded and opened up new far-reaching vistas. It is, I trust I may say, the hope of all contributors to this book, that besides being our humble tribute to Prof. Garti, it may stimulate a few readers to pursue the investigation of multiple emulsions.

Before delving into some of the most prominent works of Prof. Garti, it is apposite to say something here about Nissim—the man and scientist. In describing the biography of a distinguished scientist, there is always the challenge of balancing the personal aspects with the professional accomplishments. The reader is referred to the Preface of the first *Festschrift* for a biographical sketch of Prof. Garti, which offers a testimony to his eminence in various facets of surfactant chemistry.

It would not be in accord with Jewish ethics to tell all of a man's praise in his presence—it can be done only in part. This brief Preface is therefore not the place to expand on the personal characteristics of Nissim and the more so as some of them were detailed at the end of this Preface.

However, it is still worth reiterating Professor Garti's deep love for teaching. We know that Nissim, who is not capable of patting himself on the back, will do anything he can to evade premeditated questions intended to highlight his remarkable scientific career. Yet, were we to ask Prof. Garti what would best characterize his life's work, then, modest as he is about his multifarious achievements, he would undoubtedly prefer to emphasize that at heart he is, first and foremost, a teacher.

Presumably two reasons underlie Prof. Garti's devotion to the arduous task of education. First, learning was prized in Nissim's household, his parents striving to imbue their children with a yearning for enlightenment. Nissim still remembers that no sacrifice—including the carefree joys of childhood—was too great in the pursuit of learning. Second, Nissim has a deep and abiding respect for the teachers who directed him toward the experimental sciences. Perhaps these two reasons led Nissim to develop a commitment to the teaching profession.

In the Preface of the first *Festschrift*, we have elaborated on the inferior status of the teacher, on the way experimental work has to be done, and on the assistance tendered by Nissim to colleagues and young scientists. In the present Preface we would like to deal with two other points. First, we discuss the seemingly contradictory method of Nissim's teaching: Prof. Garti is considered a preeminent teacher, beloved by all his students without exception. It seems prima facie rather paradoxical because, after all, Prof. Garti is a very demanding and tough teacher, somewhat reluctant to give compliments or high grades. So what is the magic of Nissim?

It seems that Prof. Garti is the consummate pedagogue who teaches by personal example. Few teachers have given more of themselves to their students than Nissim. He is never too busy to help young scientists, to give them the gift of knowledge, how to proceed on the paths they had embarked upon, always with kindness and a sincere interest in them and their work. Nissim tries to help even low-performing students to cope with the myriad problems they face in their scientific work on an almost daily basis. He provides his assistance, sparing no effort and expecting no recompense.

He will juggle his hectic schedule in order to respond to others in need of advice. He is always ready to put his personal library at his students' disposal and they say that his books are frequently of more value than those of the university library. Any attempt to thank Nissim is usually a source of embarrassment to him. A teacher devoted to his students, Prof. Garti will not cancel a single lesson even if it involves great inconvenience for him. Nissim's students are impressed with his fairness and integrity, and with his scientific rigor and intellectual grasp. Those who have passed through Prof. Garti's hands can appreciate his refusal to yield to perfunctory or superficial performance as part of his instruction and research work. Above all, he invigorates his students to launch and conduct their research projects, to raise the proper questions, and to try to gain otherwise unavailable insights by employing innovative measuring techniques. Prof. Garti teaches them repeatedly that investigation yoked too tightly to a specific scientific model is almost always liable to fail. They should therefore seek less trite approaches for their apparent insoluble research problems. In a word, he encourages them to aspire to the highest standards of scientific excellence.

The legacy of a scientist is usually measured in the number of his publications. Prof. Garti thinks that the contribution of a true scientist should be valued via the students who came into his circle of influence, who learned from him, and who would be ready to emulate his way even if it is difficult to follow because of its high standards and exacting nature. We know, however, that Nissim, even after meticulously checking and testing his experimental data and their analysis again and again, always thinks that his work still lacks that perfection that would have been possible given more ample leisure. Indeed many a potential scientific paper that could readily be published was postponed or even abandoned by Nissim, since in his opinion just a certain minor point was not sufficiently well-founded. This is the reason why Prof. Garti disdains what might be called tawdry scientific methodology—hastily publishing premature articles that rely on a maze of rather implausible hypotheses with only scant experimental data behind them. Nissim asserts that it would have been salutary if the authors of such papers had noticed that in this way science does not advance in the least.

Most educators have failed to study diligently how students use their knowledge and training in out-of-classroom (or lab) settings when these may be the uses that matter most. Nissim, however, initiates his students not only into careful research but also into the practical life of the professional. For example, he instructs them how to acquire the competence and confidence to prepare

and submit articles for publication in scientific journals and how to see their works properly through the publishing process, a task that without assistance can be frustrating and discouraging even to a highly motivated student. Even when Nissim himself writes the manuscript of a scientific paper, he feels that every student who has participated in the research work is just as involved and helpful in its completion and getting it published. Moreover Prof. Garti would generously help students and colleagues with their own writing in order to achieve clarity of exposition.

The second point relates to science education. The most widely claimed goals of science education are: to produce citizens who are scientifically literate and to support citizens in understanding reports and discussions of science (especially about issues that may be controversial) that appear in the popular media. At the core of science education activity we find also two other tasks:

1. To attack pseudoscience beliefs and ideas that have been gaining ground over the last two decades, mainly because of the entertainment industry.
2. To improve the ability of the general public to distinguish between fact and fiction, since the visual media have blurred the distinction between these two concepts.

Nissim's sense of concern and commitment to the furtherance of science has always extended beyond his own students to include the "educated layman." So he does his best to achieve these goals.

As a part of his endeavor to bring academic interests and scientific achievements to a large audience and to widen the circle of informed readers and listeners, Prof. Garti is always ready to find time, whether to lecture on science to interested groups or to write scientific articles in popular journals. Nissim is endowed with an extraordinary blend of oratorical power and intellectual acuity that, together with his infectious enthusiasm and eloquent writing, almost inevitably enables him to imbue his listeners and readers with a keen interest in science. Moreover Nissim also tries to direct their attention to research findings that are rarely communicated to the general public directly by scientists.

Such lectures or papers have to be prepared carefully and thoroughly. Nissim knows how to elucidate points of cardinal significance and how to translate from scientific language into something palpable and meaningful to the "common person." Indeed Nissim's limpidity and economy of expression, combined with the restriction of technical material to the minimum, enable him to simplify intricate scientific topics.

Prof. Garti also knows how to whet the appetite of his audience for more information. In lectures he succeeds in igniting the interest of his listeners by utilizing highly entertaining and informative presentations communicated in a voluble, exuberant style. Frequently he tells vivid stories about how science works and about the strengths and frailties of prominent scientists. Far from

least, these stories reveal the significance of scientific achievements more than the usual dull reports. It should, however, be noted that Prof. Garti gets far and away the best response from his listeners and readers when he teaches them to be skeptical and to accept as truth only statements that are irrefutable through scientific scrutiny.

Nissim's solution to the prevailing problem of disgruntled listeners who pester the lecturer with questions is very typical and instructive. Most lecturers regard them as too clever by half and needing to be taken down a peg or two. Prof. Garti always tries the opposite attitude toward these smart alecs. Generally, he follows a two-pronged strategy. First, he would treat them with considerable respect and tolerance, never being invidious or talking down to them. Second, he would use his dry and witty sense of humor to relieve tension during his lectures.

We now turn to the seminal contributions of Prof. Garti to the study of multiple emulsions. Nissim's research interests could never be limited to any single scientific problem or theme, and this only becomes fully apparent upon examining the scope of his over 300 refereed publications, invited symposia, book chapters, and reviews. However, for Nissim, multiple emulsions have been a favorite object of investigation ever since the early 1980s, and he has become one of the most active scientists in this burgeoning area.

Moreover there is an interesting relation between Prof. Garti's skills as a scientist and teacher regarding multiple emulsions. It is known that persuading students to be involved in multiple emulsions research is a formidable educational challenge. Far be it for me to argue that such an investigation is too difficult for a graduate student, since the underlying concepts in multiple emulsions science are quite easy to grasp and yet experimental work on these emulsions is undoubtedly one of the most demanding and enervating research tasks students may encounter within surfactant chemistry. This is simply because the continuous, long-term (in the order of weeks and even months!) monitoring need for following up any changes in the multiple emulsion stability, and furthermore in the rate of addendum release, virtually confines the student to the lab as long as such an experiment is going on. Nevertheless, some students have been lured by Nissim's enthralling descriptions of multiple emulsions, and the main results of their M.Sc. and Ph.D. works are detailed in the following.

These multi-compartment liquid dispersions are considered adequate vehicles for controlled and sustained delivery of entrapped addenda, such as drugs. Thus a drug that is dissolved or suspended in the internal aqueous phase of a W/O/W emulsion is forced to diffuse across the oil phase prior to being released into the body fluids.

Multiple emulsions have been the subject of numerous investigations due to their importance as an emerging and promising technology for slow and controlled release of active ingredients and as a major scientific challenge regarding the preparation and improvement of the kinetic stability of these inherently thermodynamically unstable entities. As a testimony to the

evolution of the field of multiple emulsions, one may merely peruse the subject matter of the articles in this book.

Prof. Garti maintains a preeminent position in the research of multiple emulsions as is manifested by his nearly 40 articles concerning them. These scientific papers exhibit the gripping combination—typical of Nissim's research work—of brilliant and ingenious insights together with rigorous treatment of even the minutest details, which are acquired by hard and systematic experimental work.

Several highlights achieved by Prof. Garti are herewith outlined more or less in chronological order.

In 1983 Nissim had already tackled the problem of how to overcome the unpleasant taste of drugs such as chlorpromazine-HCl. Oral administration of a bitter-tasting medication to a child is obviously a cumbersome task. The solution suggested by Prof. Garti was to dissolve the drug in the inner phase and to release it throughout the oil phase in the presence of synthetic gastric juice. A child will swallow medication willfully when the outer water phase contains synthetic flavors that simulate attractive tastes such as that of strawberry or raspberry. It should be noted that the drug release in this case is neither controlled nor targeted.[2]

The release of electrolytes and drugs from multiple emulsions can, in principle, proceed via two possible mechanisms:

1. The oil layer separating the inner and outer aqueous phases behaves as a semipermeable membrane: The release of solutes from a W/O/W multiple emulsion, for instance, only occurs through breakdown of the multiple droplets as a result of osmotic flow of water to the inner phase and consequent coalescence of the droplets.
2. The oil layer behaves as a permeable membrane and the solute migrates by diffusion from the inner emulsion.

Prof. Garti has shown[3] that the diffusion mechanism is a predominant factor in the migration of electrolytes from the inner to the outer phase in multiple emulsions. The release of the electrolyte is affected by its hydrophobicity and concentration but not by the viscosity of the internal phase.

In another paper, written in collaboration with D. Whitehill,[4] it was demonstrated that the addition of NaCl to multiple emulsions causes droplet shrinkage due to loss of internal water. Micelle transport seemed to be the primary mechanism.

A kinetic model, adapted from that of Higuchi for release of dispersed drugs from polymeric matrices, was found to be suitable for the release of electrolytes from multiple emulsions. The existence of a diffusion-controlled mechanism was experimentally confirmed. This mechanism is facilitated as the concentration of reverse micelles formed in the oil phase increases.[5]

In another investigation it was shown that whereas the presence of electrolytes in the outer aqueous phase has no bearing on the control of drug leaching

from the inner aqueous phase even when there is no osmotic pressure gradient between the two aqueous phases—implying that the system is not controlled solely by this factor—the presence of electrolytes in the internal water phase can retard the drug migration. Electrolytes that can cause salting-in of the emulsifier to the oil phase strengthen the oil–water interface and thereby decrease drug transport.[6]

Additional milestones in Prof. Garti's work regarding the stabilization of multiple emulsions should be mentioned:

Solid oil (paraffin wax) is superior to liquid oil in formulations of multiple emulsions as a stable rigid oil membrane is formed that hinders the migration of additives from the inner water phase.[7]

Prof. Garti was among the first scientists to understand the significance of the replacement of monomeric surfactants (usually blends of hydrophobic and hydrophilic amphiphiles) by polymeric emulsifiers. Such multi-anchoring macromolecules provide strong steric stabilization capabilities via the formation of thick and flexible interfacial films. An early highlight of Nissim's work in this area comprises the utilization of polysiloxane-graft-poly(oxyethylene) to stabilize W/O/W multiple emulsions. Stable, small droplet size W/O emulsions were formed with hydrophobic comb-grafted copolymers adsorbed at the inner interface. The outer interface of the W/O/W multiple emulsions was stabilized by hydrophilic comb-grafted copolymers with similar structures but with high-density grafting and long poly(oxyethylene) chains. The release rates of additives from such multiple emulsions were very slow.[8] Silicone-based surfactants impart unusual mechanical stability to W/O/W multiple emulsions that makes them possible candidates for slow release systems for agricultural applications.[9]

In addition to synthetically tailor-made polymeric amphiphiles, naturally occurring biopolymers are considered for stabilization of multiple emulsions, especially where these emulsions are needed for food and cosmetic applications. Thus the protein bovine serum albumin (BSA) significantly improves the mechanical and steric stability of W/O/W emulsions when used in a blend with a nonionic surfactant, such as Span 80. It is assumed that the two amphiphiles act synergistically by forming an interfacial complex—presumably a thick, strong gelled film that confers resistance to rupture and elasticity on the inner droplets. Based on Garti's modification of Higuchi's model, it was concluded that BSA has a double role:[10]

1. At the inner phase, BSA provides a mechanical barrier to the release of small molecules from the internal interface. The release proceeds mainly via reverse micellar transport. The presence of BSA reduces the chance of reverse micelle formation and thus decreases the release rate of entrapped addenda within the emulsion droplets.
2. At the outer phase, BSA impedes coalescence via steric stabilization.

Stable water in vegetable oil emulsions can serve as basic preparations for food-grade W/O/W multiple emulsions. A novel way of stabilization of such

systems is to use submicronal α-form, crystallized hydrogenated fat (tristearin) homogeneously dispersed in the oil phase.[11] The crystals should be submicronal in size to effectively adsorb and accommodate at the interface. Large crystals flocculate in the continuous oil phase.[12] Yet these solid fat particles cannot sufficiently stabilize the W/O emulsion, and they have to be blended with a lipophilic surfactant (polyglycerol polyricinoleate, PGPR). The combination of fat microcrystals and PGPR has the following advantages:

1. Aggregation and flocculation processes are inhibited.
2. PGPR serves as a cross-linker or a bridge between the fat particles and water.
3. PGPR facilitates the anchoring of the fat particles in the oil phase while dangling itself in the water phase.
4. PGPR functions as an α-tending crystal structure modifier.

Improved stability can be obtained by utilizing the emulsifier PGPR in the internal water phase and a protein-polysaccharide hybrid (as a substitute for the common nonionic hydrophilic monomeric emulsifiers) in the external interface. For instance, whey protein isolate (WPI) forms soluble complexes with hydrocolloids such as xanthan gums or galactomannans at selected pH values and weight ratios. These hybrids with specific interface recognition capabilities stabilize multiple emulsions mainly via steric interactions at the oil-water external interface. However, at high gum levels, the emulsions become more elasticized, uncomplexed gum migrates to the bulk, and the depletion mechanism will dominate. The stabilizing effect of such hybrids is synergistic. Thus droplets of WPI/xanthan-based multiple emulsions are, respectively, one-fourth or one-eighth smaller than those of multiple emulsions based solely on either WPI or xanthan.[13]

Excellent stability to coalescence was obtained via interaction of WPI with modified pectin.[14]

The effects of WPI/polysaccharide conjugates on the stabilization of multiple emulsions are the subject of recent studies. It was observed, for example, that the release of vitamin B_1, entrapped in the core of W/O/W multiple globules, is hampered due to the biopolymer adducts formed at the interface.[15] Similar adducts stabilize O/W/O multiple emulsions and serve as efficient barriers against release of addenda contained in the inner phase.[16]

In Prof. Garti's opinion, employing multiple emulsions should not be restricted to pharmaceuticals, nutraceuticals, and cosmetics. He hopes that other promising and exciting applications will be available in near future. The microencapsulation of fine boron particles in W/O/W multiple emulsions may serve as such a feasible example.[17]

Last, the results of a very recent investigation concerning a novel type of multiple emulsion, dubbed "emulsified microemulsion" (EME), are herewith

shown. Since the kinetic stability of the internal phase is inversely proportional to its droplet size, it is conceivable that nanosized droplets (microemulsions) would improve the system stability. One potential application of such emulsified microemulsions is the formation of submicronal injectable liquid W/O/W preparations for controlled drug release.

This concept has barely been implemented before now due to the tedious experimental work necessary to ascertain that the nano-droplets remain intact after the secondary emulsification stage as well as after prolonged storage. Moreover the very fast exchange of the monomeric surfactants between the internal and external interfaces induces concurrent emptying of the core phase and leaching of the inner water phase.

This second problem has been solved skillfully in Prof. Garti's lab by using glycerol monooleate as surfactant, R(+)-limonene/ethanol 1:1 (by weight) as the oil phase, and water/glycerol (9.15:0.85) (wt/wt) as the water phase. Samples of this microemulsion were further emulsified, utilizing the hydrophobic graft copolymer Pluronic F127 (PEO_{99}-PPO_{67}-PEO_{99}, where PEO stands for polyethylene oxide and PPO for polypropylene oxide). Pulsed-gradient-spin-echo NMR has shown that glycerol monooleate and R(+)-limonene are present in the inner phase of the emulsified microemulsion even after the second emulsification process. Electrical conductivity measurements have demonstrated that at least 60 wt% of the internal water phase remained confined after the second emulsification stage. SAXS (small angle X-ray scattering) measurements have shown that the inner microemulsion in the emulsified microemulsion is more ordered than the original L_2-phase. This surprising finding may be attributed to the effect of the polymeric surfactant. Cryo-TEM (transmission electron microscopy) images of the emulsified microemulsion provide direct evidence for the existence of spherical globules in the inner phase, having a mean diameter of 250 ± 50 nm in rather good agreement with corresponding results by DLS (dynamic light scattering): approximately 200 ± 50 nm, which is about 10 to 20 times smaller than the size of conventional multiple emulsion globules. The investigated system has remained stable during up to 12 months of storage at ambient temperature. This promising system is now being studied to explore its ability to retain bioactive addenda and release them in a controlled manner.[18]

It seems appropriate to conclude with a personal note. Prof. Garti is to me a teacher and a mentor. The scope and magnitude of his influence on me are without equal. As a senior member of Nissim's research team, I have a daily contact with him, and I would like to share some of my impressions with the readers of this Preface. Prof. Garti is now at the pinnacle of his highly variegated scientific achievements. As Nissim enters his seventh decade of life, I can assure the readers that he has not yielded to the demands of age. On the contrary, every year Nissim looks younger. None of his stamina has been lost. His energy and willpower may be likened to an ever-flowing fountain and, more wonderful still, they show no signs of diminishing. Prof. Garti's

enthusiasm for work, his alert response to new ideas, and his original insights have remained unblemished and keen. He is always the first person to enter the lab in the morning and the last to leave at night, filling his long day with incessant activity.

Nissim never forgets to acknowledge that all his accomplishments and success are due to his wonderful family and, most of all, to his wife, Ricki. She has been standing by Nissim in joy and sorrow, always giving of herself without stint to him and their family.

This *Festschrift* is herewith presented to you, Nissim, as a token of our heartfelt appreciation and admiration. The book is accompanied by our ardent prayer that like our ancient leader, Moses, may "your eyes remain undimmed and your vigor unabated." It is the fervent hope of your friends, colleagues, and students that you will enjoy good health and continuous creative labor for many years to come.

ABRAHAM ASERIN, Ph.D.

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INTRODUCTION TO MULTIPLE EMULSIONS TECHNOLOGY AND APPLICATIONS: AN UPDATE

When it was decided to compile a book in honor of Prof. Nissim Garti on the occasion of his sixtieth birthday, choosing an appropriate topic was rather difficult. The diversity of topics investigated by Prof. Garti and his research group in the surface chemistry field is simply amazing. A most conspicuous theme among these topics is the area of multiple emulsions in which Nissim has become a foremost authority. Moreover this attractive subject provides a good prospect for much demand even if the technology is still waiting for a real breakthrough.

Since William Seifriz described for the first time in 1925 these intricate liquid systems having ternary, quaternary, or more complex structures that he named multiple emulsions, the literature has been "flooded" every year with tens of new examples demonstrating release patterns and control of active ingredients using these systems. Multiple emulsions, at least in theory, have significant potential in many applications because the internal droplets can serve as an entrapping reservoir for active addenda that can be released by a controlled transport mechanism. Many of the potential applications would be realized in the fields of agriculture, pharmaceuticals, cosmetics, and food.

In practice, double emulsions consist of large and polydispersed droplets that are thermodynamically unstable, with a strong tendency for coalescence, flocculation, and creaming.

Efforts have been made to improve emulsion stability and to control the release of active matter. Almost any possible blend of low-molecular weight emulsifiers, oils, cosolvents, and coemulsifiers have been tested. The nonviscous fluid multiple emulsions were always unstable. Only semisolid multiple emulsions, gelled or thickened systems, have long shelf-life and prolonged stability. Biopolymers, synthetic graft and comb copolymers, and polymerizable emulsifiers impart steric or mechanical stabilization to the multiple emulsions and significant controlled release of additives contained in them. Naturally occurring and synthetic macromolecular surfactants that increase the viscosity of each phase of the multiple emulsion and form complexes with the emulsifiers or the oil can lead to formation of systems that will behave much like microcapsules, microspheres, and mesophasic liquid crystals.

This book mostly stresses the recent findings that model the transport phenomena through the different interfaces present in multiple emulsions. It will be useful for each formulator to understand how he can enhance the stability