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LARGE-SIZE MONODISPERSE LATEXES AS A COMMERCIAL SPACE PRODUCT

By Dale M. Kornfeld
Space Sciences Laboratory

August 1977

NASA



*George C. Marshall Space Flight Center
Marshall Space Flight Center, Alabama*

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16. ABSTRACT Dr. John W. Vanderhoff of Lehigh University has proposed Orbital Flight Tests and Spacelab experiments leading to the production of large-size (2 to 40 μ m diameter) monodisperse latexes in microgravity. Explanations are given as to why monodisperse particles in this size range are not currently available. The four main topics discussed are: (1) the potential uses of these large particle size latexes, (2) why it is necessary for the particles to have a very narrow size distribution, (3) why large amounts of these monodisperse latexes are needed, and (4) why it is necessary to go to microgravity to prepare these latexes.					
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LARGE-SIZE MONODISPERSE LATEXES AS A COMMERCIAL SPACE PRODUCT

INTRODUCTION

This report provides background information on a proposed Space Processing experiment which is being considered as a payload to be carried aboard the Space Shuttle in Orbital Flight Test (OFT) and Spacelab configurations.

Dr. John W. Vanderhoff, Lehigh University, has submitted space flight proposals to NASA in response to NASA Announcement of Opportunity No. OA-77-3 and OPPI-76-1. Dr. Vanderhoff proposes to develop an experimental chemical reactor to be flown in OFT, and then a production reactor to be flown in Spacelab. The OFT reactor would attempt to demonstrate the feasibility of performing seeded emulsion polymerizations in microgravity to synthesize monodisperse polystyrene latexes in particle size ranges much larger than it is possible to prepare on Earth. The Spacelab reactor would be a production facility suitable for synthesizing these monodisperse latexes in quantities sufficient for sale to hospitals and research institutions.

DISCUSSION

For some years, the Dow Chemical Company has sold monodisperse latexes in small samples for instrument calibration and in quantities of a few gallons for serological diagnostic tests. Monodisperse latexes are those in which the particle size distribution is extremely narrow. The first latex particle test was for rheumatoid arthritis, and a review published 5 years later contained 78 references to the use of latexes for this purpose. By 1973 the annual sales of latex particle diagnostic kits amounted to \$ 30 million.

Presently, monodisperse polystyrene latexes are available in the size range of 0.1 μm to approximately 2 μm . However, monodisperse particle sizes larger than 2 μm , with an acceptably small standard deviation, are generally

not available except in very small amounts. A standard deviation of approximately 1 percent or less would be considered acceptable. The particle size range between 2 μm and approximately 40 or 50 μm (at which point latex particles can be separated by sieving or elutriation) is the size range in which Dr. Vanderhoff proposes to manufacture monodisperse latexes in microgravity.

There is a great demand for monodisperse latex particles within this size range. Dow Chemical and Polysciences, Inc. have expressed interest in marketing such particle sizes when they are available (Appendices A and B). The current sales price at Dow is \$ 50 for 15 ml of 5 percent solids latex, or \$ 67 000/kg (\$ 30 000/lb) of polymer. Sizes larger than 2 μm would command much higher prices.

Several companies presently supply latex particles for instrument calibration and for research use:

1. Dow Chemical supplies monodisperse latexes in the particle size range of 0.09 to 2 μm at approximately 2 percent or less standard deviation, depending on size. Dow also supplies larger particle size latexes but does not claim them to be monodisperse; for example, they produce a 7.8 μm average diameter particle latex, but it has a standard deviation of 2.8 μm .
2. Polysciences, Inc. supplies monodisperse latexes in the same general range of sizes as does Dow but only up to approximately 2 μm .
3. Particle Information Services, Inc. supplies a wide selection of latexes, but does not claim that any in their 2 to 40 μm size range are monodisperse. For example, their 2.02 μm latex, at 0.7 percent standard deviation, is indeed monodisperse, but their 3.8 μm particles have a standard deviation of 21.0 percent; 4.5 μm particles have 22 percent; and 7.3 μm particles have 12.4 percent, etc.
4. Rhone-Poulenc (France) offers monodisperse latexes in sizes up to 2.5 μm .
5. Duke Scientific of Palo Alto, California, does not produce its own particles but simply repackages particles bought from Dow or elsewhere. The May 1977 issue of their catalog/price list claimed availability of 5, 10, and 20 μm size particles at 1.4 to 1.6 percent standard deviation. However, Dr. Vanderhoff examined samples of each of these sizes, which he bought from

Duke, and found that their actual standard deviations were in the range of 20 to 45 percent. Therefore, Duke's claim to be able to supply monodisperse latexes in the 2 to 40 μm size range is apparently not substantiated. Dr. Vanderhoff has recently completed his study of these Duke particles and plans to present his results to Duke so their advertisement can be corrected. (Appendix C consists of Dr. Vanderhoff's particle count data and optical microscope photographs of Duke's particles together with his addendum letter which includes the electron microscope photographs.)

Seeded emulsion polymerization is the only technique known at present by which monodisperse latexes can be produced in usable quantities; however, even this technique is only effective in producing particles up to approximately 2 μm in diameter. Dr. Vanderhoff has prepared very small amounts of monodisperse latexes of 3.0 and 5.6 μm diameter for experimental use (the stable residue from polymerizations that produced mostly coagulum), but they have never been offered for sale because their preparation was not reproducible.

During recent discussions concerning Dr. Vanderhoff's proposal to produce these monodisperse latexes in space, in the 2 to 40 μm size range, the following four questions had to be answered repeatedly:

1. What are the potential uses of these large particle-size monodisperse latexes?

The greatest benefit of the preparation of the 2 to 40 μm diameter monodisperse latexes would be in the research that their availability would stimulate. The very small amounts of latexes in this size range that were prepared by Dr. Vanderhoff have been used to good advantage, e.g., in a study of glaucoma. The exit channels of human eyes were sized accurately — 1.2 μm and smaller particles perfused through the exit channels without hindrance; 1.8 and 3.0 μm sizes perfused but with some hindrance; and the 5.6 μm size did not perfuse at all. Besides this glaucoma work, other research groups used them to size other pores in the body as well as to test the efficiency of filters.

The use of these particles can be divided into two main categories: (1) calibration standards for various instruments and (2) standards to determine pore size.

Since most hospitals and clinics in the U.S., and in other countries, use one or more Coulter Counters (or a similar instrument by another maker) for blood cell counts, and since the available calibration standards are not

completely satisfactory, all of these hospitals and clinics are potential customers for these larger size latexes. Even though they use another calibration standard at present (namely a much smaller size monodisperse latex), virtually all would discontinue this present material in favor of a larger size monodisperse sample.

However, one of the more exciting potential uses of these large monodisperse latexes is in cancer research. For example, Dr. Marion LeFevre and coworkers at the Medical Research Center, Brookhaven National Laboratory, have been using the largest size monodisperse polystyrene latex presently available ($2\ \mu\text{m}$) in their cancer research (Appendix D). This particular research concerns the carcinogenic nature of asbestos fibers which are found in the drinking water of certain large cities. The latex particles are being used to determine pore size of the stomach and intestinal walls and the tendency of foreign particles to penetrate these pores and enter body tissue. This information can be used to determine just how dangerous certain size carcinogenic particles can be when ingested with drinking water, that is, whether or not they remain in the body or pass through and, if they do remain, where they come to rest; and will they eventually perfuse back out, or is their retention irreversible and cumulative. It is presently known that the $2\ \mu\text{m}$ particles are irreversibly retained in the body, but larger size particles cannot be studied because none are available.

Dr. Vanderhoff is presently submitting a proposal with Brookhaven to the National Institutes of Health in another example of cancer research using large monodisperse latexes. This proposed line of research would include attaching carcinogenic chemicals or materials onto or inside the latex particles and then allowing the latex particles to perfuse through the body and to eventually congregate at some point. That is, the latex would be a selective carrier for a carcinogen, and the size of the latex particle would determine where the carcinogen was deposited so that its effect on a specific part of the body could be studied. If the chemical anthracene were used to tag certain size latex particles, another benefit would result from the fact that anthracene will fluoresce under ultraviolet light, thus making the latex particles even more clearly visible in the tissue. Again, this research must await the availability of larger size monodisperse latex.

Some years ago, Dr. Lane Allen of the Medical College of Georgia measured the pore size of the peritoneal cavity membrane in laboratory animals. Since monodisperse samples were not available, he used the styrene-divinylbenzene copolymer particles of relatively broad distribution and attempted to distinguish those sizes that went through and those sizes that did not. His results were not completely definitive because the monodisperse particles were not available.

These particles may also find uses in serology as substrates for immunological diagnostic tests. At present, polystyrene particles with sizes ranging from $0.2 \mu\text{m}$ to approximately $1 \mu\text{m}$ are used for this purpose to prepare test kits. Generally, sizes in the range 0.5 to $1 \mu\text{m}$ are preferred for these tests because sizes smaller than $0.5 \mu\text{m}$ give less sensitive tests and the sizes larger than $1 \mu\text{m}$ are less available. The $2 \mu\text{m}$ size monodisperse particles are available in only small quantities because of the difficulty of their preparation in the Dow pilot plant. Particle sizes above $2 \mu\text{m}$ simply are not available.

The availability of larger particle sizes would make their evaluation for serological reaction uses possible. Advantages of these large particle-size latexes would include their better visibility (which would make the agglutination easier to detect either in a test tube or on a slide) and their better comparison with the fixed red blood cells they are intended to replace. For this application, however, the particles should be of a density close to that of the intended medium so that the test kits would have suitable shelf stability on Earth. This could be accomplished by copolymerization of a suitable ratio of tert-butylstyrene and vinyltoluene instead of styrene. The most important point, however, is that the use of these particles will be stimulated by their availability. As experience has shown concerning the uses of smaller particles, the publication of research using the particles stimulates other researchers to inquire as to their availability and to order them for their own research. The success of a space preparation would be sufficient advertisement to start demand, which will grow exponentially as research publications appear.

2. Why is it necessary for the latexes to have such a narrow particle size distribution?

This question might be rephrased as: Why is it necessary for a yardstick to be exactly 36 in. long, instead of 36.5 in., or some other number. The reason is that the yardstick is used as a standard to measure other objects; therefore, it is necessary that its length be exactly the same as all other yardsticks.

Monodisperse latex particles are also used as standards to measure various other objects. Therefore, the latexes used for calibration should have as narrow a particle size distribution as is reasonably possible. For example, the first monodisperse latex of $1.2 \mu\text{m}$ diameter prepared by Dr. Vanderhoff had a standard deviation of 150 \AA . This sample certainly was sufficiently narrow in particle size distribution to be used as a calibration standard. However, further

research decreased the standard deviation of this particle size to 50 Å, a significant reduction that improved the value of this sample. Further research to obtain further decreases in standard deviation must be considered in view of the fact that the electron microscope measurements have a limit of accuracy of 20 to 30 Å, so a further significant decrease in standard deviation would approach the limit of accuracy of the measurements and hence is not as desirable or important as the decrease from 150 to 50 Å.

Another example is the calibration of Coulter Counters and other electronic particle counters used to count red blood cells. Almost every hospital and diagnostic laboratory in the country uses one of these instruments to perform their blood cell counts. Since the instrument depends upon the proper operation of its electronic components, which can and do drift with time, it is necessary to calibrate it periodically. The presently available calibration standards include (1) 2 μm monodisperse polyvinyltoluene particles, (2) styrene-divinylbenzene copolymer spheres (Dow) which have an average diameter of 7.8 μm but a standard deviation of 2.8 μm, and (3) ragweed pollen spores which are roughly spherical and relatively monodisperse but with hooks and projections extending from their surface. None of these samples are completely satisfactory as a calibration standard because the 2 μm monodisperse particles are much smaller than the 7 μm red blood cells which the instrument counts, the 7.8 μm styrene-divinylbenzene copolymer particles are the proper size but their size distribution is too broad, and the ragweed pollen spores are too large and their surface aberrations make their hydrodynamic behavior questionable. The obvious solution is to prepare a monodisperse sample of approximately 7 μm average diameter. A standard deviation of 1 percent or less would be considered acceptable.

The conclusion is that the monodispersity should be as good as can be obtained with a reasonable expenditure of effort.

3. Why is it necessary to prepare such large amounts of various monodisperse latexes (which can be accomplished only in space) when one small sample bottle should last a long time, even for a large hospital?

In the first place, the amounts Dr. Vanderhoff proposes to prepare in microgravity are actually small compared with the demand. The present proposal describes an apparatus for carrying out four consecutive seeded emulsion polymerizations, three of which would amount to 1500 ml and the fourth, 2000 ml. If these latexes contained 30 percent solids (which is a realistic figure), the amounts of polymer would be, respectively, 450 and 600 gm. In addition, part of the 2000 ml batch might be used as a seed for the next series to be run in

microgravity. Presumably, the largest particle size that can be prepared easily on Earth would be used as the seed for the first series in microgravity, and several series would be contemplated. Therefore, let us compare the 450 gm batches with what has been made earlier.

The monodisperse latexes sold by Dow are made in 20 gal reactors except for those sizes for which there is a greater demand; these are made in a 200 gal reactor. The 20 gal reactor produces 60 lb of polymer, of which 20 lb may be used as seed for the next batch, and the other 40 lb are sold. The corresponding numbers for the 200 gal reactor are 600 lb total and 400 lb for sale.

Originally Dr. Vanderhoff prepared monodisperse latexes smaller than $2\ \mu\text{m}$ in his laboratory in 2 liter batches, which would yield 600 gm to 1 kg of polymer, and gave these first latexes to interested scientists. However, while he offered these samples as gifts, not for sale, he repeated the preparation in 20 gal batches. These batches lasted for several years, but when demand grew so large that the latexes had to be sold instead of given away, the better selling sizes had to be prepared in 200 gal reactors.

The very small samples of monodisperse latexes Dr. Vanderhoff prepared in the size range 2.0 to $5.6\ \mu\text{m}$ were made in capped bottles (the stirred reactors were unsuitable for the preparation). These bottles had a capacity of 100 to 200 ml, which corresponds to 20 to 60 gm of polymer; due to certain stability problems, the bottle size could not be effectively scaled-up. Since these polymerizations produced significant amounts of coagulum, the yields were much less than theoretical estimates. Consequently, these research samples could be prepared only on a very limited basis.

If only one researcher, or one hospital, were to use these large-size monodisperse latexes, a few grams might suffice; however, consider 100 researchers, each with a sample bottle containing 5 gm of solid polymer, which would amount to 500 gm. Therefore, the production yield of 450 gm of polymer, which is what one Spacelab flight of excellent yield would produce, would be enough for less than 100 samples and, therefore, an inadequate supply for the scientific community.

Dr. Vanderhoff anticipates, and states in his proposal, that the proposed production reactor would be capable of preparing sufficient polymer for initial distribution to the scientific community. As this material is used, the demand for

It will grow, and other flights will be required to meet this demand. Eventually the demand will grow to the extent that it will be worthwhile to scale-up the Spacelab production reactors five- to ten-fold in capacity.

If some simple estimates are made of the probable demand for just one size ($7\ \mu\text{m}$) monodisperse particle latex, not for research but simply for Coulter Counter calibration in hospitals and clinics, then it quickly becomes apparent that large dollar figures are involved. Consider 20 000 hospitals and/or clinics just in the U.S. and an additional 25 000 or 30 000 in the rest of the world (probably a very conservative estimation), and that each hospital has several Coulter Counters and each clinic has at least one. Also consider that the Coulter Counter manual directs that each instrument must be calibrated at least once a month (and generally once a week); and from experience consider that usually about half of each sample bottle is lost through spillage, drying out, etc., due to the less than excellent laboratory technique of the technician doing the red blood cell counts. Therefore, each of the approximately 50 000 hospitals or clinics could need one small bottle of standard $7\ \mu\text{m}$ latex per year on the average. If each bottle contained 5 gm of solid polymer then 1000 lb of polymer would be needed each year. Even if these estimates are twice too high, half that required amount of polymer would still be 500 lb per year. Since Dow currently sells their small size, easily made monodisperse latexes at \$ 30 000/lb, the cost of 500 lb amounts to \$ 15 million per year, every year, just for a Coulter Counter calibration standard.

It is also noted here that Duke Scientific Corporation, Palo Alto, California, advertises their "monodisperse" latexes in the 5, 10, and $20\ \mu\text{m}$ size range for \$ 35/5 ml at a concentration of 5×10^6 particles/5 ml bottle (Appendix C). This amounts to \$ 13 000/gm, or \$ 6 million/lb.

4. Why is it necessary to go to microgravity to prepare these larger size monodisperse latexes?

Large-size monodisperse latexes are prepared by first preparing a monodisperse latex of relatively small particle size (which is relatively easily done), and then using this latex as a "seed" to grow the particles to a larger size. Monomer and initiator, as well as a carefully controlled amount of emulsifier, are added to the seed latex, and the polymerization is carried out to completion at the desired temperature. The control of emulsifier concentration is critical because if too high it gives a new crop of particles and if too low it gives coagulum.

If a new crop of particles is formed, the latex is ruined. The formation of coagulum reduces the amount of latex produced and may range from a large sticky lump to sand-like particles that can be filtered from the latex. Sometimes the latex coagulates completely to form a large lump of coagulum and a clear serum, although this is relatively rare.

At relatively small particle sizes (0.2 to 0.4 μm), there is a relatively safe emulsifier concentration range, that is, the range in which the coagulum is minimal yet no new particles are initiated. However, as the particles are grown to larger and larger sizes in successive seeding steps, this range becomes more and more narrow until at 1 to 2 μm sizes it can go either way, i. e., duplicate polymerizations may give either a relatively unstable monodisperse latex or a stable latex with a new crop of particles.

The principal reason for the instability of the large particle-size monodisperse latexes is the tendency of the particles to settle or cream upon standing. The critical size for settling of polystyrene particles (density 1.050 gm/cc) in water is 0.65 μm . It can be proven experimentally that polystyrene particles of 0.8 μm or larger diameter slowly settle out upon standing, while particles of 0.5 μm or smaller diameter never settle out. Therefore, the larger the particle size of the latex, the greater the tendency to settle. This tendency can be offset by agitation, and almost all emulsion polymerizations are stirred more or less rapidly to give mixing of the ingredients and good heat transfer. However, too great a stirring rate can also give coagulation of the latex particles, particularly if they are swollen with monomer and are "sticky."

The theory of coagulation of colloidal sols can be divided into two classifications: diffusion-controlled and agitation-induced flocculation. In a given case, both mechanisms are operative, but generally diffusion-controlled flocculation is predominant at particle sizes of approximately 0.1 μm , while at particle sizes of approximately 1.0 μm , each mechanism is about equally operative, and at particle sizes much larger than 1 μm , agitation-induced flocculation is predominant. This means that in a stirred system, the formation of coagulum by flocculation of the particles to form relatively small aggregates proceeds by diffusion until these aggregates grow to approximately 1 μm in size, after which their growth becomes autoaccelerating and they quickly become very large.

Thus, the larger the particle size, the greater the tendency for the particles to settle during polymerization and, hence, the greater the formation of coagulum. The particles sold by Dow are monodisperse latexes in the size

range 0.09 to 2 μm , and one of the techniques they use to facilitate production of the larger size is to go to a lower density particle. Their 1.2 μm particles are polystyrene, but their 2 μm particles are polyvinyltoluene (density 1.027 gm/cc). The reason for this is that the slightly lower density of polyvinyltoluene makes it a little easier to prevent flocculation.

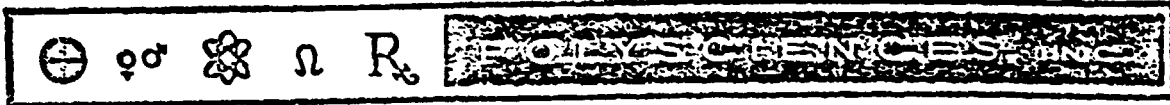
The tendency for large latex particles to settle is not the only factor in determining the latex stability. If it were, the problem could be solved by preparing particles of density 1.00 gm/cc. In fact, Dr. Vanderhoff accomplished this by preparing particles from a vinyltoluene-tert-butylstyrene mixture that gives a polymer of density 1.00 gm/cc. However, this does not solve the problem because of the density difference between monomer and polymer. This difference causes the density of the growing latex particles to change during polymerization and results in a tendency of the polymer particles, which are swollen with low-density monomer, to cream during the first part of the polymerization and then settle during the latter. It has also been suggested that heavy water be used to replace normal water as the medium in which to perform the emulsion polymerization. At first thought, it would appear that the higher density of heavy water (1.1056 gm/cc) would help prevent settling of the particles, and indeed it would. However, during the earlier stages of conversion, the tendency of the growing particles to cream would be much higher. The cost of producing approximately 100 gal batches of latex using heavy water would be prohibitive, especially when it is realized that most, if not all, of the heavy water could not be recovered for reuse but would have to remain with the latex.

Another very important factor in determining latex stability is that with increasing particle size, the particle surfaces become crowded with ionic groups which hinder the adsorption of oligomeric radicals. The latexes are prepared with various emulsifiers such as alkyl sulfates, alkyl aryl sulfonates, sulfonated succinic acid esters, etc., which absorb on the particle surfaces. Also, the persulfate ion initiator which is used introduces additional anionic surface groups. Since the surface/volume ratio decreases with increasing particle size, the larger size particles have a higher concentration of surface sulfate endgroups. Calculations show that the concentration of these surface sulfate groups become quite large at particle sizes above 1 μm . Too high a concentration of surface sulfate groups means that the oligomeric radicals may not be able to adsorb as soon as they are formed; and if they cannot adsorb on a particle surface, they will continue to grow in the aqueous phase until their chain length exceeds the critical length for solubility and they precipitate from the aqueous phase to nucleate a new particle. Thus new particles can be formed from persulfate initiator, particularly at large particle sizes, as well as by an excess of emulsifier.

Therefore, the major problem in preparing large particle-size monodisperse latexes is that their particle sizes exceed the range in which the colloidal and surface properties determine the behavior of the system and enter the range in which the bulk properties determine the behavior. Appendix E contains photographs of 0.4 μm diameter monodisperse polystyrene latex particles.

The preparation of these latexes in microgravity would obviate the settling and creaming problem that diminishes their colloidal stability. Also, the polymerizations could be carried out under conditions (such as certain concentrations of initiator and emulsifier) that would result in unstable latexes on Earth but would proceed properly in microgravity and not result in formation of a new crop of particles.

APPENDIX A



PAUL VALLEY INDUSTRIAL PARK, WARRINGTON, PENNA., 18976 PHONE 215-343-6484

October 19, 1976

Dr. John W. Vanderhoff
Associate Director-Coatings
Center for Surface and Coatings Research
Francis MacDonald Sinclair Memorial Laboratory
Lchigh University
Bethlehem, Pa. 18015

Dear John:

I was pleased to learn from our conversation that you have the possibility of making monodisperse latex particles in ranges greater than the limiting ranges of 2-3 microns which we now are able to make available. I think that this will be an extremely useful size range as it bridges a gap that exists now. As you well know, small particles can be readily made with a variety of functionalities and the like. Larger particles in the range of 25 microns and above likewise can be made and these can be reasonably well separated by sieving techniques. Certainly above 50 microns suspension particles are readily separable in reasonably good classification. It is in this lower in between range that the principal deficiency exists. I think that a very definite research and commercial need will be fulfilled if you are able to successfully do this. We, as marketers of monodisperse latex particles, would find a ready commercial application for these materials. I look forward to your success in this matter.

Sincerely,

POLYSCIENCES, INC.

B. David Halpern, Ph.D.,
President

BDD/mg

APPENDIX B



DOW CHEMICAL U.S.A.

November 2, 1976

MICHIGAN DIVISION
MIDLAND, MICHIGAN 48640

Dr. John W. Vanderhoff
Center for Surface and
Coatings Research
Lehigh University
Bethlehem, PA 18015

Dear John:

I understand you are contemplating research toward making large uniform particles in the 2-40 μ m diameter size range.

We would be interested in learning about your results as we believe that there is a significant market for particles in this size range. They are needed for calibrating instruments like the Coulter Counter[®], for determining pore sizes and efficiency of filters, and they may be useful as carriers for biochemicals as in the diagnostic technique of solid-phase radioimmunoassay.

We might be interested in adding such particles to our present line of products. Please keep me informed as to your progress. Good luck.

Sincerely,

Reigh B. Bangs

Reigh B. Bangs, Ph.D.
Central Research
Plastics Laboratory
1702 Building

Ph: (517)-636-1200

st

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DOW CHEMICAL U.S.A.

February 4, 1977

MIDLAND, MICHIGAN 48840

Dr. John W. Vanderhoff
Associate Director
Center for Surface & Coatings Research
Francis MacDonald Sinclair Memorial Lab
Building 7
LEHIGH UNIVERSITY
Bethlehem, PA 18015

Dear John:

Thanks for your letter of December 16, 1976. We are indeed interested in your proposal, it just takes time to get feedback from all concerned on a thing like this.

Dow would be interested in assuming responsibility for the manufacture and marketing of these large-particle-size monodisperse latexes, if the project proves to be technically and economically feasible.

Good luck on your project. Please keep me informed as to the progress of the proposal.

Sincerely,

Leigh B. Bangs, Ph.D.
Central Research
Plastics Laboratory
1702 Building

Ph: (517)-636-1209

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APPENDIX C



Lehigh University Bethlehem, Pennsylvania 18015

CENTER FOR SURFACE AND COATINGS RESEARCH

Francis MacDonald Sinclair Memorial Laboratory — Building #7

JOHN W. VANBRUNOFF,
Associate Director - Coatings

July 5, 1977

Dale M. Kornfeld
ES-73
NASA-MSFC
Marshall Space Flight Center, Alabama 35812

Dear Dale:

The following are preliminary results of particle size determinations of the 5, 10, and 20 μ m-diameter polystyrene latexes sold by Duke Scientific Corporation. It is our understanding that, when our proposal "Production of Large-Particle-Size Monodisperse Latexes" was reviewed, one member of the reviewing committee produced a sample of the Duke particles, with the remark that there was no need to produce large-particle-size monodisperse latexes in microgravity because Duke had already accomplished it on earth. The Duke brochure states that the standard deviations of these samples are 1.4-1.6% of the diameters for the 5, 10, and 20 μ m particles. As will be shown below, these standard deviations are completely false -- the samples are not monodisperse and the actual standard deviations are much greater than the stated values. Moreover, the most casual optical microscopic examination shows that the samples are not monodisperse.

The Millipore Particle Size Analyzer, which was interfaced with the optical microscope, was used to determine the particle size distribution of all three samples at magnifications of 100X and 400X. The particle size printouts, the mean particle size, and the mean standard deviations are enclosed for your information. You will note that the number of particles counted were 500 for the 10 and 20 μ m particles and 100 for the 5 μ m particles. The percentage of standard deviation varied from about 20% to 40%, which by far exceeds the values of 1.4% to 1.6% cited in the Duke Scientific catalogue. Furthermore, the presence of submicron particles could be detected by visual observation but were too small to be sized by the Analyzer interfaced with the optical microscope. A slide of the 5 μ m particles was prepared and viewed in the electron microscope. The results indicated the presence of a high concentration of particles in the submicron range. These results have to be verified in order to establish that the grid used in sample preparation was not contaminated. As a matter of fact, we expect in the next two weeks to run a complete analysis of all three samples for particle size distribution in the submicron range by interfacing the Millipore Particle Size Analyzer with the electron microscope. A report will be written up as soon as this analysis is complete.

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Duke's Polystyrene Microspheres
Cat. No. 271
Size 20.18 μ m; 1.3% RSD

13.0	17.0	17.0	18.0	17.0
19.0	17.0	19.0	18.0	16.0
19.0	17.0	5.0	0.0	20.0
20.0	18.0	15.0	19.0	18.0
20.0	20.0	19.0	17.0	23.0
18.0	19.0	4.0	20.0	21.0
18.0	21.0	15.0	15.0	20.0
21.0	20.0	19.0	18.0	20.0
19.0	20.0	19.0	18.0	18.0
20.0	19.0	19.0	19.0	19.0
19.0	19.0	21.0	14.0	19.0
19.0	6.0	21.0	20.0	20.0
19.0	19.0	22.0	14.0	20.0
19.0	19.0	20.0	19.0	18.0
18.0	20.0	20.0	20.0	19.0
21.0	14.0	21.0	19.0	20.0
21.0	21.0	21.0	19.0	17.0
18.0	17.0	19.0	19.0	21.0
20.0	19.0	20.0	19.0	19.0
19.0	20.0	16.0	17.0	19.0
20.0	18.0	19.0	19.0	20.0
19.0	19.0	15.0	19.0	20.0
19.0	20.0	16.0	15.0	18.0
21.0	19.0	21.0	19.0	9.0
20.0	10.0	1.0	19.0	18.0
7.0	14.0	20.0	11.0	19.0
17.0	19.0	19.0	19.0	20.0
20.0	19.0	10.0	15.0	21.0
19.0	18.0	20.0	19.0	20.0
3.0	19.0	10.0	14.0	20.0
21.0	18.0	18.0	18.0	20.0
14.0	19.0	20.0	19.0	20.0
19.0	19.0	20.0	19.0	19.0
19.0	16.0	13.0	19.0	15.0
19.0	18.0	20.0	15.0	19.0
5.0	17.0	20.0	19.0	19.0
18.0	17.0	18.0	15.0	19.0
19.0	19.0	20.0	18.0	19.0
18.0	19.0	19.0	17.0	19.0
14.0	14.0	18.0	20.0	19.0
17.0	19.0	19.0	19.0	19.0
17.0	19.0	18.0	18.0	19.0
19.0	17.0	19.0	18.0	16.0
			19.0	

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16.0	13.0	23.0	18.0	15.0
19.0	19.0	20.0	19.0	19.0
18.0	19.0	21.0	13.0	20.0
18.0	16.0	8.0	19.0	17.0
11.0	18.0	21.0	18.0	18.0
17.0	18.0	21.0	4.0	19.0
20.0	15.0	16.0	21.0	21.0
11.0	19.0	21.0	21.0	21.0
20.0	19.0	19.0	17.0	19.0
20.0	19.0	20.0	19.0	17.0
21.0	19.0	22.0	21.0	19.0
21.0	18.0	21.0	17.0	16.0
19.0	19.0	21.0	18.0	21.0
20.0	19.0	18.0	22.0	21.0
19.0	20.0	21.0	21.0	17.0
4.0	20.0	20.0	8.0	16.0
20.0	22.0	21.0	20.0	20.0
21.0	21.0	20.0	20.0	20.0
8.0	21.0	20.0	13.0	11.0
12.0	21.0	21.0	17.0	20.0
18.0	20.0	21.0	16.0	21.0
6.0	21.0	5.0	22.0	14.0
20.0	21.0	20.0	21.0	20.0
20.0	20.0	6.0	18.0	20.0
17.0	20.0	20.0	21.0	20.0
23.0	21.0	15.0	19.0	19.0
21.0	21.0	19.0	19.0	17.0
19.0	21.0	20.0	20.0	15.0
1.0	6.0	4.0	21.0	19.0
18.0	20.0	21.0	19.0	18.0
7.0	21.0	18.0	5.0	19.0
19.0	20.0	16.0	9.0	22.0
19.0	20.0	19.0	13.0	19.0
19.0	21.0	20.0	20.0	18.0
20.0	20.0	21.0	20.0	17.0
6.0	19.0	19.0	21.0	6.0
19.0	18.0	19.0	19.0	20.0
19.0	19.0	20.0	15.0	18.0
19.0	17.0	21.0	19.0	18.0
19.0	19.0	21.0	19.0	20.0
19.0	18.0	19.0	21.0	21.0
16.0	19.0	18.0	18.0	19.0
21.0	21.0	18.0	21.0	21.0
11.0				19.0

(Concluded)

18.0	19.0
20.0	19.0
16.0	20.0
21.0	19.0
7.0	15.0
20.0	19.0
20.0	12.0
18.0	19.0
19.0	12.0
18.0	2.0
19.0	0.0
19.0	21.0
19.0	19.0
18.0	20.0
20.0	21.0
13.0	19.0
19.0	17.0
19.0	19.0
10.0	16.0
21.0	22.0
20.0	20.0
21.0	21.0
21.0	15.0
21.0	19.0
18.0	16.0
18.0	15.0
20.0	19.0
20.0	18.0
19.0	3.0
21.0	
21.0	
7.0	
1.0	
20.0	
21.0	
21.0	
3.0	
23.0	

Total Count	500.
Mean	17.83 μm
Variance	16.51
STD Deviation	4.06 μm
% STD Deviation	22.8%

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Duke's Polystyrene Microspheres

Cat. No. 270

Size 10.08 μm ; 1.5% RSD

10.0	7.0	10.0	10.0	6.0
8.0	8.0	10.0	10.0	8.0
8.0	8.0	10.0	9.0	9.0
8.0	8.0	10.0	10.0	6.0
10.0	9.0	10.0	8.0	10.0
10.0	9.0	10.0	7.0	10.0
11.0	7.0	10.0	8.0	10.0
10.0	8.0	10.0	10.0	10.0
17.0	10.0	10.0	10.0	10.0
9.0	7.0	10.0	9.0	10.0
4.0	10.0	10.0	10.0	9.0
11.0	6.0	9.0	8.0	9.0
10.0	5.0	10.0	10.0	9.0
10.0	8.0	10.0	10.0	10.0
10.0	10.0	6.0	9.0	9.0
10.0	9.0	10.0	9.0	11.0
6.0	7.0	9.0	10.0	11.0
10.0	8.0	10.0	10.0	9.0
10.0	8.0	11.0	11.0	10.0
9.0	8.0	13.0	10.0	10.0
10.0	8.0	11.0	10.0	9.0
10.0	8.0	9.0	8.0	10.0
8.0	9.0	16.0	7.0	10.0
9.0	8.0	7.0	10.0	17.0
9.0	8.0	0.0	10.0	10.0
10.0	8.0	9.0	10.0	10.0
10.0	9.0	9.0	11.0	10.0
8.0	8.0	10.0	10.0	8.0
10.0	8.0	8.0	9.0	8.0
10.0	10.0	10.0	10.0	11.0
8.0	10.0	8.0	10.0	10.0
10.0	10.0	10.0	10.0	11.0
10.0	10.0	10.0	11.0	9.0
9.0	10.0	10.0	10.0	10.0
8.0	10.0	9.0	10.0	8.0
9.0	0.0	10.0	8.0	13.0
10.0	10.0	10.0	8.0	10.0
9.0	9.0	10.0	10.0	10.0
10.0	10.0	9.0	8.0	10.0
9.0	10.0	10.0	10.0	11.0
10.0	10.0	9.0	9.0	9.0
10.0	10.0	10.0	9.0	12.0
10.0	10.0	8.0	10.0	10.0

(Continued)

10.0	8.0	15.0	10.0	10.0
8.0	10.0	3.0	9.0	
5.0	2.0	10.0	12.0	10.0
10.0	5.0	10.0	9.0	
7.0	9.0	10.0	0.0	10.0
10.0	8.0	10.0	5.0	
10.0	10.0	6.0	7.0	9.0
10.0	8.0	10.0	7.0	
10.0	10.0	8.0		10.0
10.0	11.0	2.0	10.0	
9.0	9.0	10.0		7.0
9.0	10.0	9.0	3.0	
10.0	7.0	10.0	8.0	10.0
10.0	10.0	9.0	8.0	
10.0	10.0	10.0	6.0	10.0
8.0	10.0	9.0		
12.0	4.0	10.0	5.0	10.0
10.0	10.0	8.0		
9.0	10.0	10.0	8.0	8.0
10.0		10.0	8.0	
10.0	8.0	8.0	8.0	12.0
10.0	12.0	10.0	8.0	
10.0	10.0	10.0	11.0	10.0
8.0	10.0	7.0	10.0	
9.0	10.0	10.0		10.0
9.0	10.0	10.0	7.0	
9.0	10.0	5.0	10.0	10.0
10.0	10.0	10.0	8.0	
10.0	10.0	8.0	9.0	8.0
8.0	11.0	8.0		
9.0		8.0	8.0	7.0
11.0	10.0	11.0		
9.0	10.0	10.0	10.0	10.0
9.0		10.0		
10.0	10.0	10.0	10.0	7.0
10.0	9.0	6.0		
10.0	10.0	10.0	10.0	10.0
10.0	10.0		10.0	
9.0	10.0	10.0		10.0
9.0	9.0	10.0	10.0	
6.0	9.0	9.0	8.0	9.0
16.0	8.0	6.0		
38.0	10.0	9.0	9.0	8.0
		10.0		

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10.0	9.0	8.0	3.0
10.0	10.0	10.0	10.0
			7.0
10.0	8.0	10.0	8.0
			10.0
9.0	9.0	4.0	8.0
		10.0	8.0
9.0	10.0		9.0
		8.0	8.0
10.0	10.0		8.0
	10.0	8.0	10.0
9.0			9.0
	7.0	10.0	8.0
10.0			19.0
	8.0	10.0	9.0
14.0			9.0
	9.0	8.0	10.0
			10.0
10.0	10.0	9.0	8.0
8.0			6.0
	9.0	10.0	10.0
10.0			10.0
	8.0	10.0	10.0
10.0			10.0
	8.0	8.0	10.0
8.0			10.0
	8.0	4.0	15.0
6.0			6.0
	10.0	8.0	10.0
10.0			8.0
	10.0	10.0	20.0
10.0		10.0	
	10.0	10.0	10.0
9.0			
	8.0	8.0	10.0
8.0		8.0	10.0
	11.0	8.0	
9.0		10.0	8.0
	10.0		
9.0		10.0	
	8.0		
10.0	8.0	10.0	

Total Count	500.
Mean	9.26 μm
Variance	5.35
STD Deviation	2.31 μm
% STD Deviation	24.9%

Duke's Polystyrene Microspheres

Cat. No. 269

Size 5.05 μm ; 1.6% RSD

5.8	5.6	5.2
4.7	5.2	5.4
3.4	4.0	5.2
4.8	5.2	4.0
5.3	5.2	4.8
5.7	5.1	2.6
3.8	5.1	5.8
1.6	6.1	5.7
5.7	5.1	5.4
5.5	4.5	4.0
5.5	5.1	6.0
5.2	5.8	7.0
5.8	5.9	3.0
5.7	5.4	4.6
5.0	5.5	5.3
2.8	0.5	5.9
5.9	0.4	5.3
5.5	0.4	4.5
4.6	0.5	5.4
4.4	0.8	5.8
4.4	0.8	5.7
5.3	0.5	5.3
3.4	0.5	3.1
5.3	0.5	5.5
4.9	0.3	5.7
4.3	0.4	5.2
5.1	0.5	5.2
4.4	0.5	3.8
5.3	0.5	
4.8	0.4	
5.8	0.3	
6.2	4.9	
5.9	5.7	
5.3	5.2	
5.4	4.2	
5.6	5.3	

Total Count	100.
Mean	4.30 μm
Variance	3.47
STD Deviation	1.86 μm
% STD Deviation	43.26%

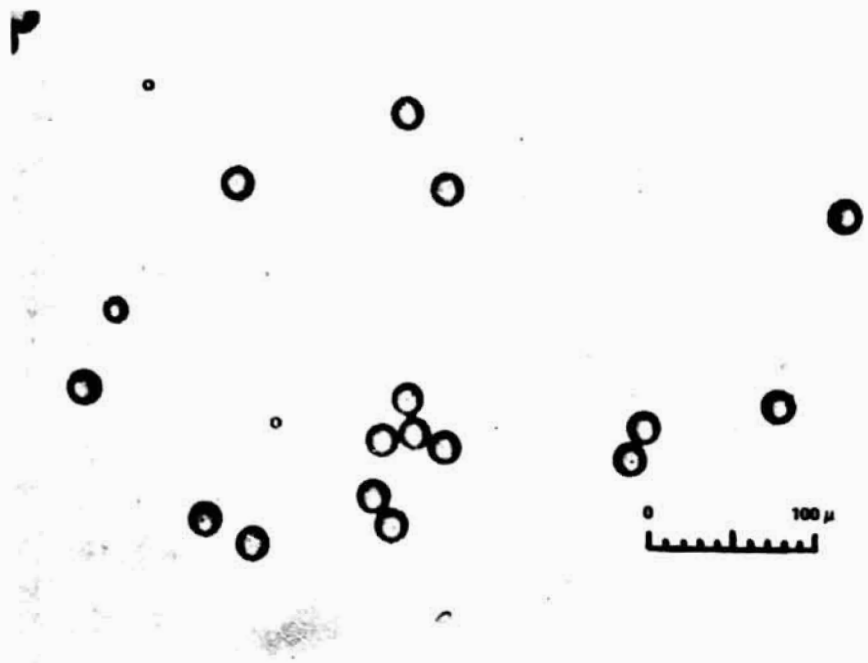
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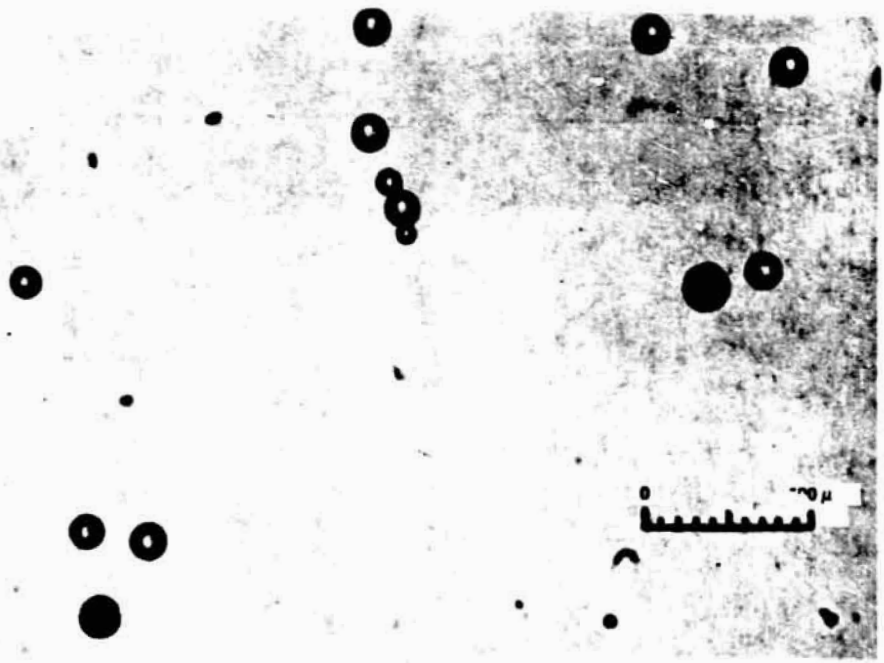
20 μ LATEX



20 μ LATEX

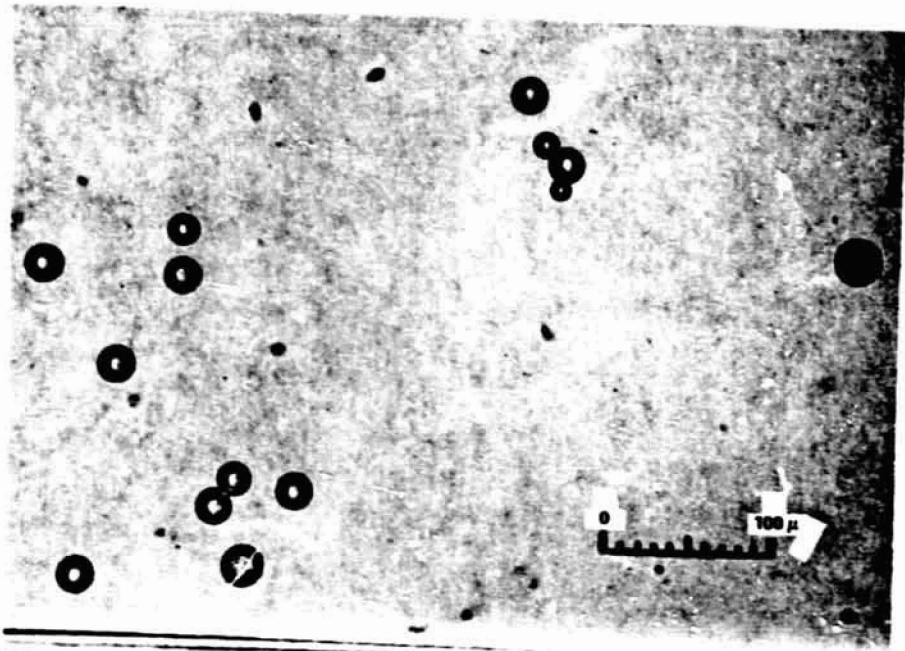


20 μ LATEX

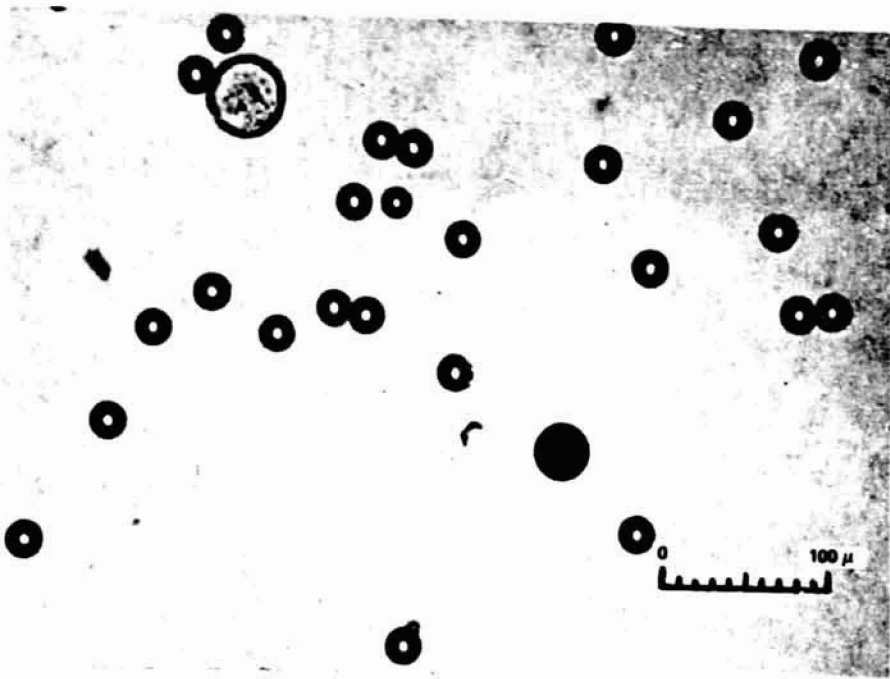


20 μ LATEX

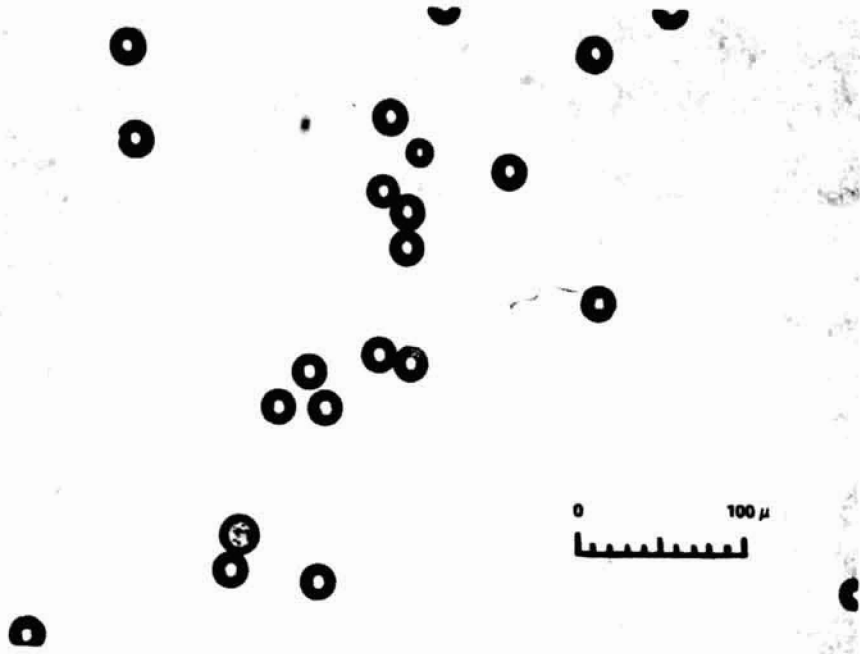
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20 μ LATEX



20 μ LATEX

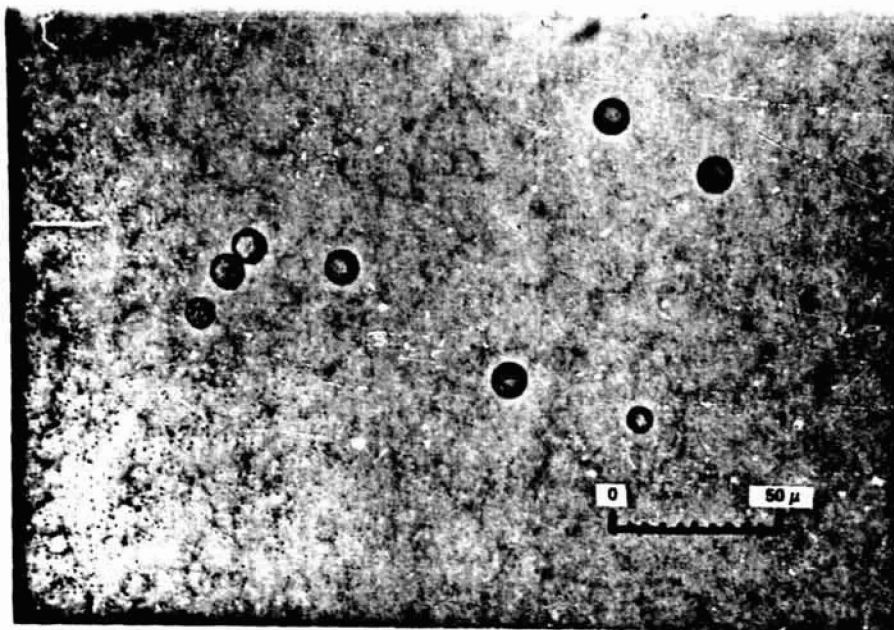


20 μ LATEX



20 μ LATEX

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10 μ LATEX



5 μ LATEX



Lehigh University Bethlehem, Pennsylvania 18015

CENTER FOR SURFACE AND COATINGS RESEARCH

Francis MacDonald Sinclair Memorial Laboratory — Building #7

August 5, 1977

Dale M. Kornfeld
8205 Louis Drive S. E.
Huntsville, Alabama 35802

Subject: Addendum to letter of July 5, 1977 (D. M. Kornfeld, ES-73)

Dear Dale:

The 5, 10 and 20 μm -diameter polystyrene latexes sold by Duke Scientific Corporation were analyzed for particle concentrations in the sub-micrometer range by transmission electron microscopy. A sample of the results are shown in the enclosed photographs which include two pictures from each sample. All three samples show the presence of sub-micrometer diameter particles at number concentrations which exceed the concentrations of the specified diameter particles. An interesting feature of the Duke polystyrene beads is that they appear to be much softer than, for example, the polystyrene beads prepared by Dow or in our laboratory. This conclusion is arrived at by the fact that the Duke particles tend to melt and become distorted in the presence of the electron beam. One explanation is that the polymerization of monomer is not complete.

The presence of the high concentrations of sub-micrometer particles in the Duke samples is surprising because these particles could be effectively removed from the large particles by elutriation methods. The problem is not the separation of very large particles from very small particles, but rather the separation of particles which are close in size. For example, a latex dispersion in the 20 μm range with a standard deviation of 20% could be improved, in terms of monodispersity, to a standard deviation of about 10% by elaborate elutriation methods. Methods have not been devised, to our knowledge, which are capable of improving the degree of monodispersity beyond this point.

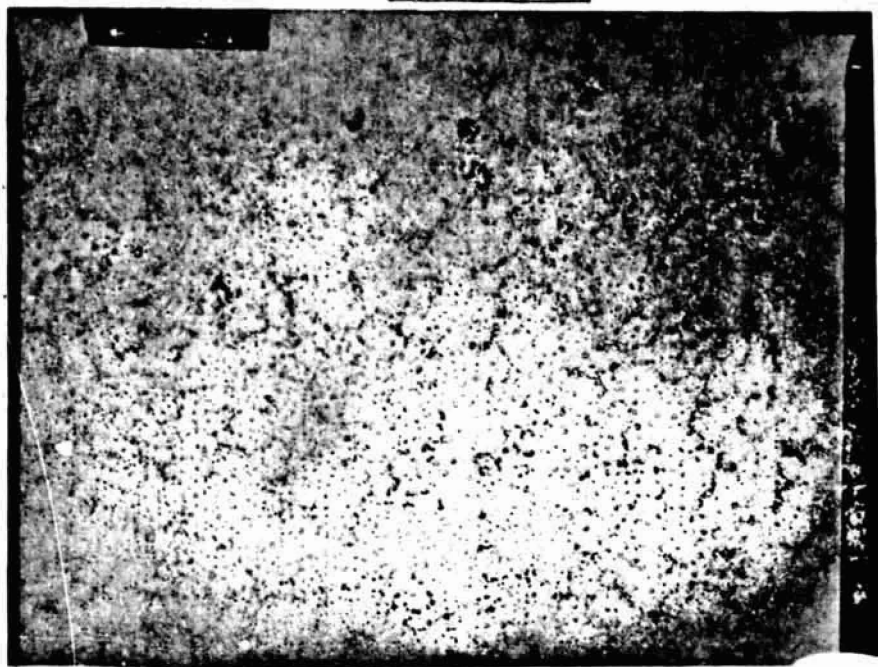
Sincerely,

John W. Vanderhoff

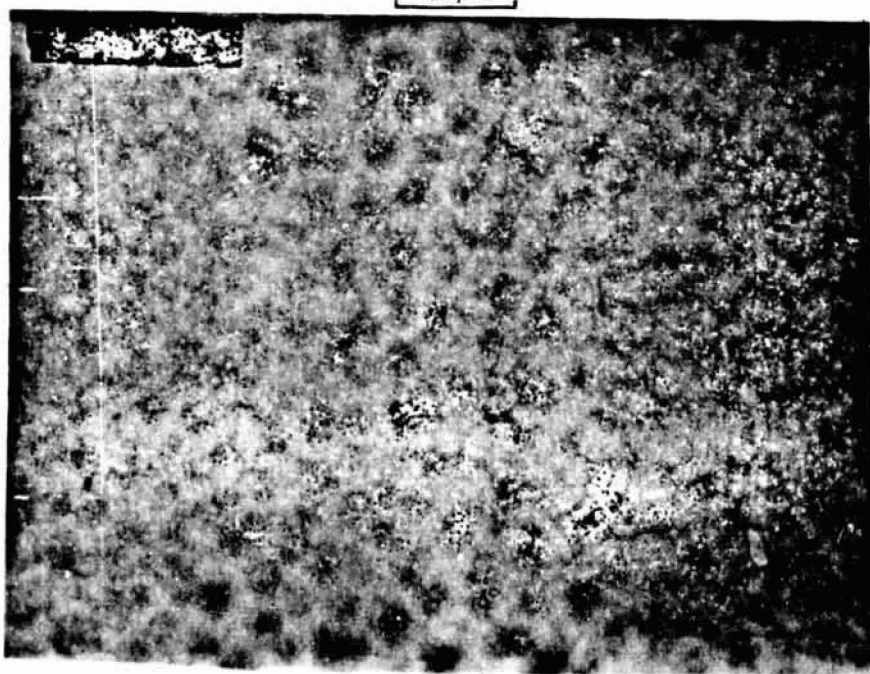
JWV:eam

Enclosure

20 μ LATEX x 2.2 K

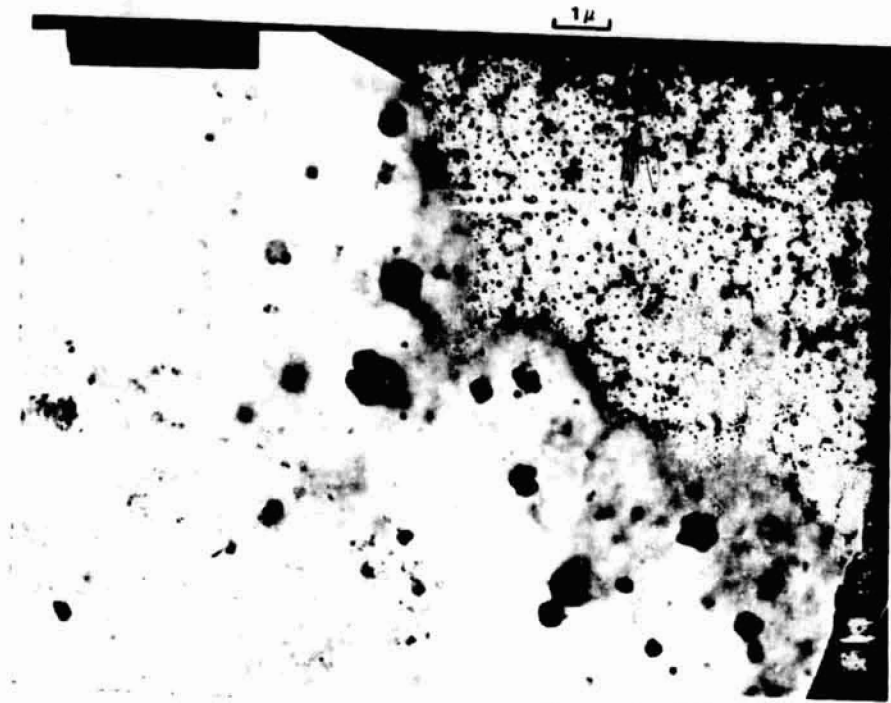


20 μ LATEX x 130 K

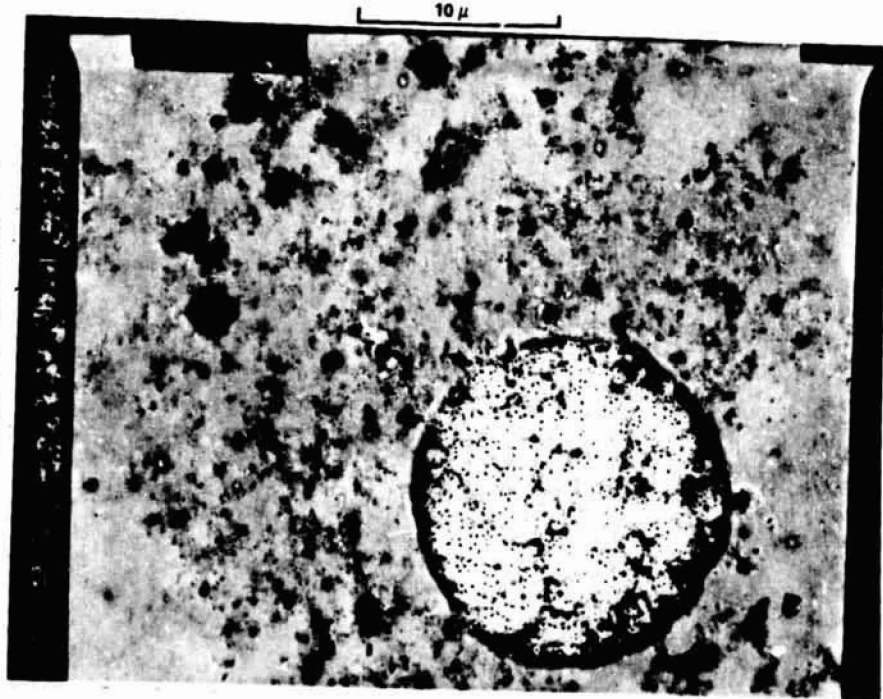


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10 μ LATEX x 6.3 K



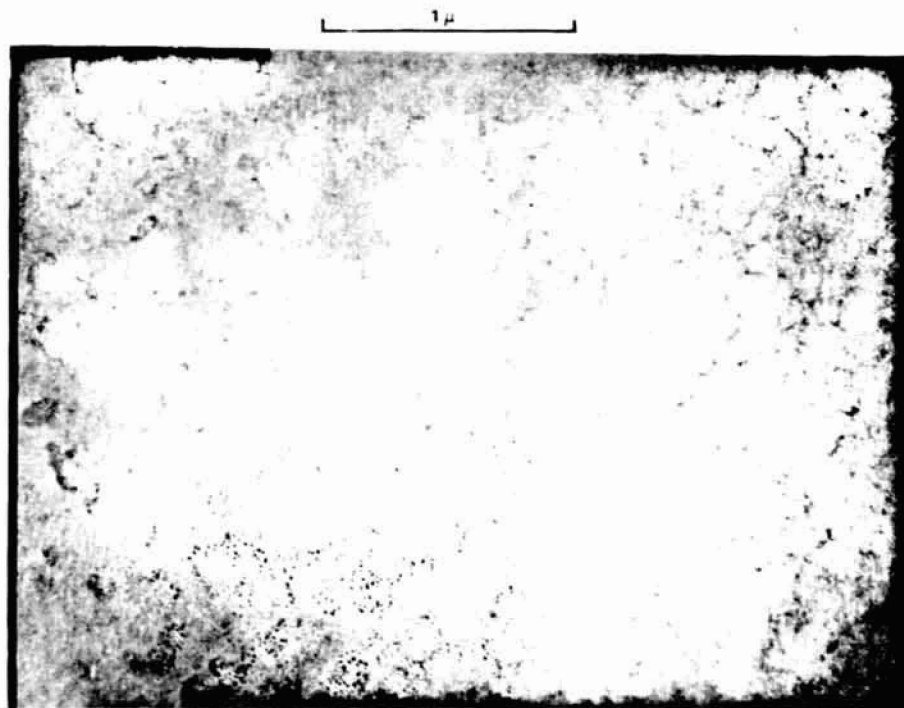
10 μ LATEX x 2.2 K



5 μ LATEX x 28 K



5 μ LATEX x 28 K



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APPENDIX D

ACCUMULATION OF 2- μ m LATEX PARTICLES IN MOUSE PEYER'S PATCHES DURING CHRONIC LATEX FEEDING

by

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J. A. Laissue**, and D. D. Joel

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Brookhaven National Laboratory
Upton, New York 11973

*Center for Surface and Coatings Research, Lehigh University, Bethlehem,
Pennsylvania 18015.

**Pathologisches Institut, Kantonsspital, CH-6000 Luzern, Switzerland.

Please address correspondence to: M. E. LeFevre, Ph. D.
Medical Research Center
Brookhaven National Laboratory
Upton, New York 11973

The epithelium of gut-associated lymphoid tissues (GALT; Peyer's patches, appendix, sacculus rotundus) appears to be a route by which small inert particulates pass the mucosal barrier of the mammalian intestinal tract [1,2]. Previous morphological studies have described the migration of carbon, trypan blue, and ferritin particles into the GALT [3-7]. These particulates are small, less than $0.1 \mu\text{m}$ in diameter, and were seen with the light microscope because of their accumulation into aggregates. The present communication describes the penetration of the mouse Peyer's patch epithelium by much larger particles, namely latex spheres of $2 \mu\text{m}$ diameter. These particles resist chemical degradation in the intestine and are large enough to be seen and counted with the light microscope permitting a semiquantitative assessment of their uptake and distribution. The results indicate that many thousands of latex particles accumulated in Peyer's patches during chronic feeding of mice with latex suspensions. Furthermore, many of the particles were retained for more than 6 weeks after the cessation of latex feeding.

Three water suspensions of polyvinyltoluene latex (mean particle diameter \pm s. d., $2.020 \pm 0.0135 \mu\text{m}$; particle density, 1.027) containing 0.94, 0.094, and 0.0094 percent solids were given as drinking fluid to three groups of 11 week-old female Swiss mice. The mice were given free access to the suspensions and to standard pelleted mouse food. The latex suspensions were given for 61 days followed by a period of 2 weeks on plain water. A control group was given tap water to drink. No attempt was made to determine the amount of latex ingested by each mouse; however, the volume of fluid consumed by the four groups did not appear to differ. All mice gained weight normally and appeared healthy.

Uptake and retention of latex in Peyer's patches were demonstrated histologically in preparations of whole Peyer's patches and in methacrylate-embedded thin sections. Eighty whole Peyer's patches were cleared in KOH and glycerol [8] and examined with a wide-field inverted microscope. Latex was unaffected by the clearing process, and individual particles could be seen at different levels in the tissue. Each patch consisted of 2-3 follicles; the dome [9] of each follicle of latex-fed mice characteristically showed an accumulation of latex particles in its center. Figure 1 shows such an accumulation in a Peyer's patch from a mouse fed the highest concentration of latex. Near the mucosal surface particles were distributed singly or in small clusters while at the mucosal surface latex was seen mostly in aggregates around the periphery of the follicle. Patches from mice given lower concentrations of latex had fewer particles and smaller aggregates. Cleared patches from control mice contained

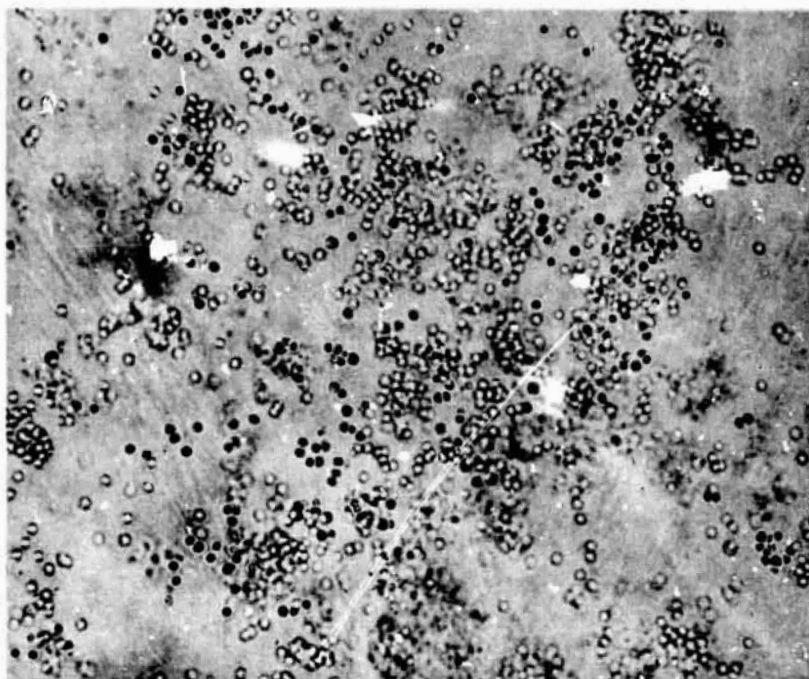


Figure 1. Two-micron latex particles within the dome of a cleared Peyer's patch follicle. Black circles are latex particles above the plane of focus. Dark shadows are large aggregates of latex below the plane of focus. Fibrous strands are a visible remnant of original tissue structure. 550X.

no particulates resembling $2\ \mu\text{m}$ latex particles. Latex particles were still visible in diminished numbers in cleared Peyer's patches 6 weeks after termination of latex ingestion.

The location of latex in relation to cellular elements could not be determined in cleared preparations, but in plastic-embedded sections the particles were seen to be associated with macrophages (Fig. 2).

Table 1 lists the numbers of latex particles recovered from intestinal tissues of the three groups of mice from which latex was withheld 2 weeks before sacrifice. The entire small intestine was rinsed in saline, separated into Peyer's patch and non-Peyer's patch tissue, weighed, minced, and placed in

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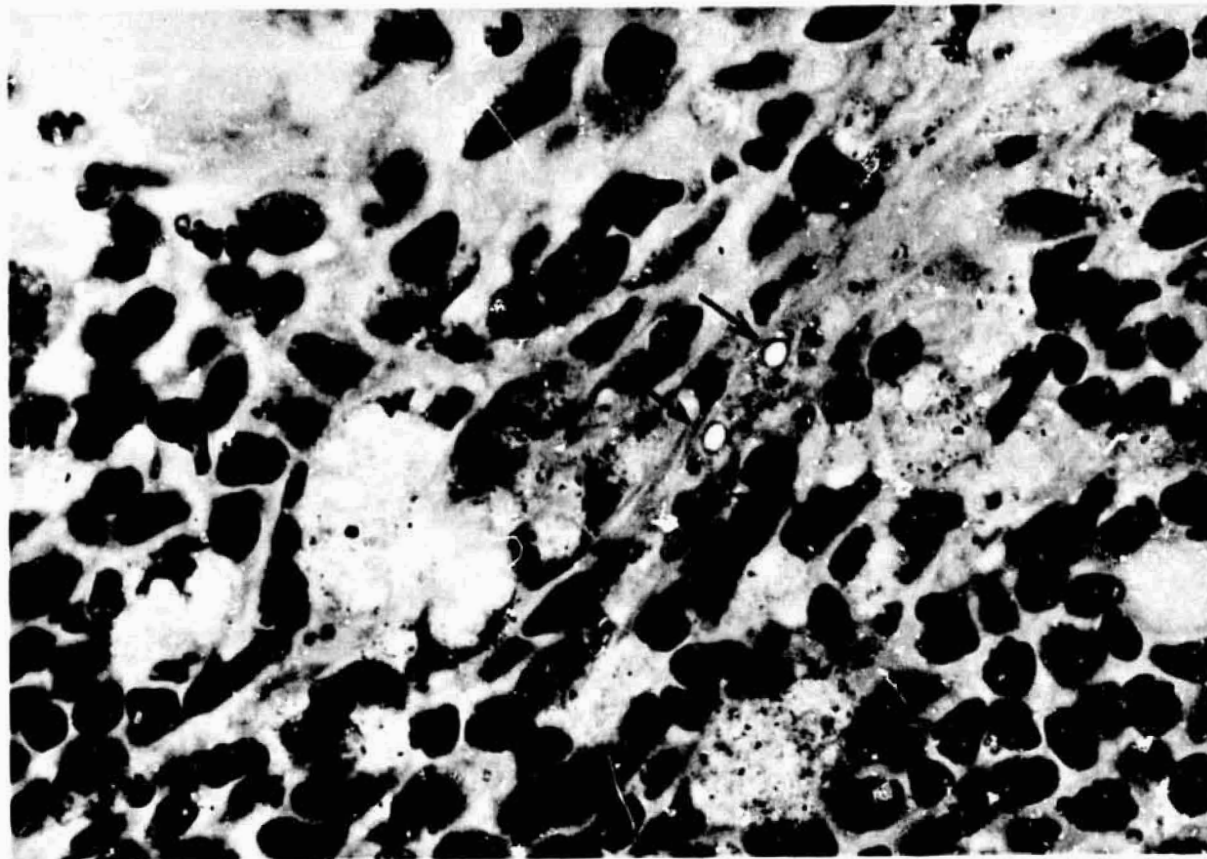


Figure 2. Two-micron latex particles (arrows) within a macrophage process in a mouse Peyer's patch. Distortion of the particles from spherical shape is due to the action of methyl methacrylate which partially dissolves latex during the embedding process. Dark lymphocyte nuclei are visible together with several pale macrophages containing other partially visible latex particles. Section was taken near the serosal surface of a Peyer's patch from a mouse given a suspension of latex as drinking fluid for two months. Giemsa. 1500X.

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TABLE 1. QUANTITATIVE DETERMINATION OF LATEX RECOVERED FROM PEYER'S PATCHES AND REMAINDER OF SMALL INTESTINE

Latex Suspension Fed (% Solids)	N	Peyer's Patches		Remainder of Small Intestine	
		Weight (g)	No. Particles $\times 10^{-5}$	Weight (g)	No. Particles $\times 10^{-5}$
0.94	15	0.054 ± 0.016	2.13 ± 0.66	1.062 ± 0.248	1.78 ± 0.58
0.094	15	0.056 ± 0.013	1.42 ± 0.98	1.078 ± 0.227	1.04 ± 0.29
0.0094	15	0.045 ± 0.008	0.18	1.005 ± 0.176	<0.05

Values are mean \pm s. d.

plastic test tubes containing 10 ml of 3 percent KOH. The tubes were agitated until the tissue was completely digested. The material was then centrifuged, washed in water, and the latex recovered by ultracentrifugation of the sediment through a linear density gradient of 0 to 20 percent urea. Particles which banded at the same level as known latex were recovered by syringe and an aliquot counted using a Neubauer chamber and an optical microscope. Additional aliquots were deposited on 0.8 μ m Nucleopore filters, rinsed with water, and examined at 5000X by scanning electron microscopy. The recovered material contained spheres identical to the stock latex; these were not found elsewhere in the gradient. Sediments of control tissues centrifuged through the density gradient showed no banding of particles at the latex level. Table 1 shows that Peyer's patch tissue comprised only a small fraction of the weight of the small intestine, but contained the major portion of the latex. The pattern of uptake was that of incomplete saturation. The location of the latex found in the remainder of the intestine has not yet been determined.

These studies indicate that inert particulates of considerable size can cross the mucosal barrier overlying Peyer's patches in intact animals. We estimate that each ml of 0.94 percent latex contained 2.7×10^9 particles and that mice given this concentration ingested approximately 7×10^{11} particles in the 61 day test period. Thus the number of particles recovered from intestinal tissue was an extremely small fraction of the number ingested. Nevertheless, when viewed in the perspective of environmental and human health problems, the uptake and retention of even a few particulates by the intestine may be of great importance if the particulates are toxic, mutagenic, or carcinogenic.

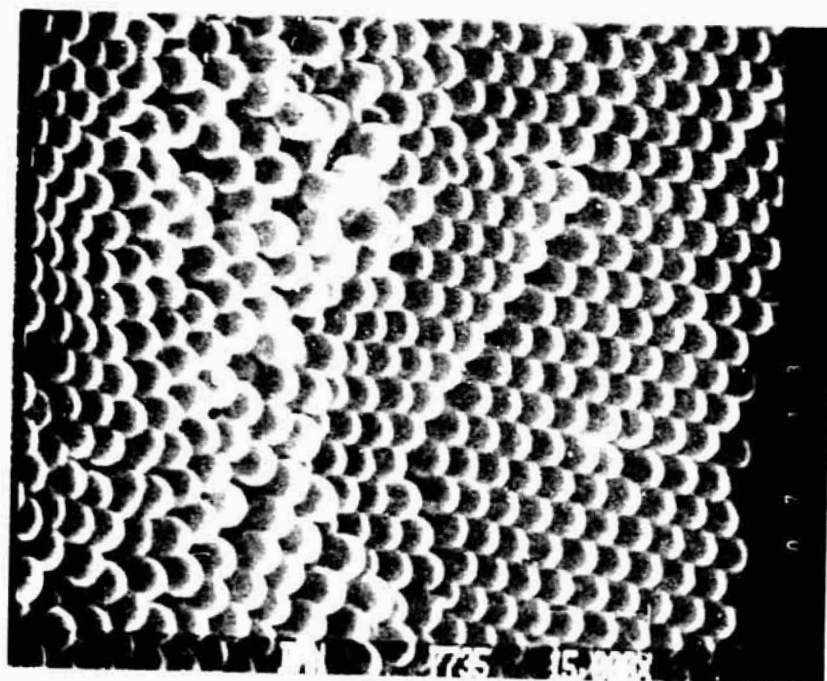
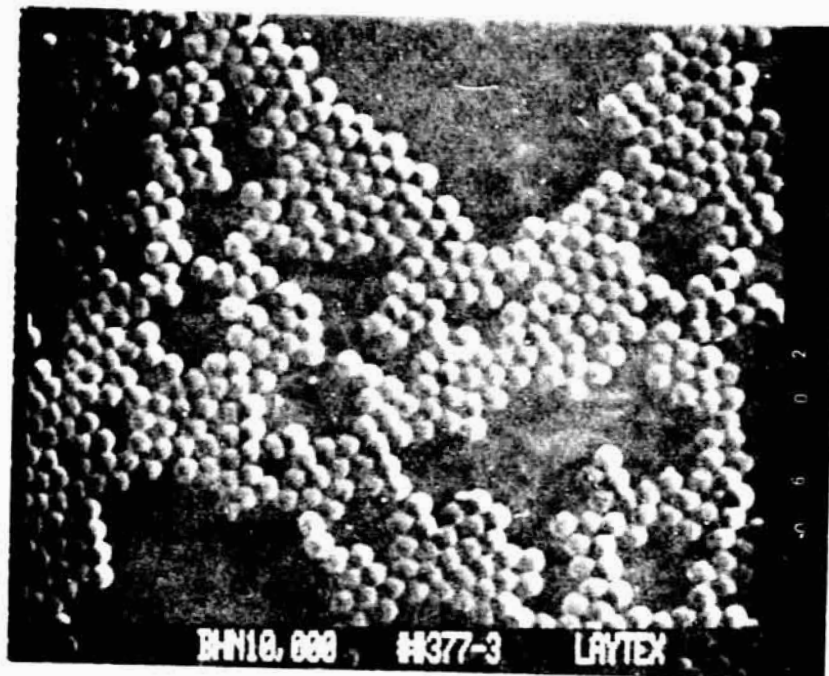
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APPENDIX E

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Photographs of 0.4 μm diameter monodisperse polystyrene latex particles prepared by Dale M. Kornfeld directly from the monomer using a one-stage emulsion polymerization at NASA/ Marshall Space Flight Center's Space Sciences Laboratory.

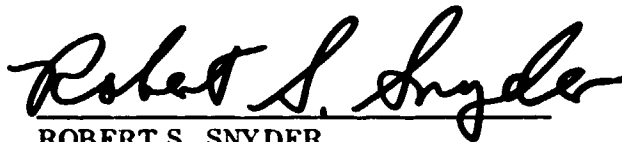
APPROVAL

LARGE-SIZE MONODISPERSE LATEXES AS A COMMERCIAL SPACE PRODUCT

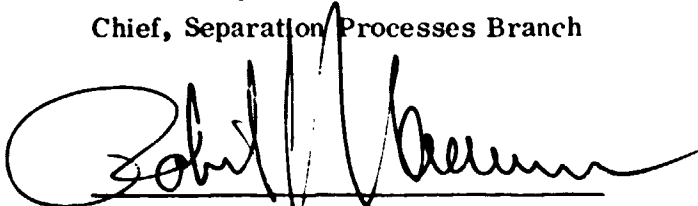
By Dale M. Kornfeld

The information in this report has been reviewed for security classification. Review of any information concerning Department of Defense or Atomic Energy Commission programs has been made by the MSFC Security Classification Officer. This report, in its entirety, has been determined to be unclassified.

This document has also been reviewed and approved for technical accuracy.



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