

## New Intravenous Drug Therapies Possible Due To Microfluidizer® Processing

Thanks in part to the Microfluidizer processor, doctors can administer new kinds of drugs to patients — drugs that previously could not be absorbed through the digestive tract and could not be administered by injection without risking the blockage of blood vessels. Earlier work with the Microfluidizer processor has already allowed patients to receive intravenous dosages of insoluble fatty oils, giving them more energy during convalescence and prompting faster recoveries. The new study, involving intravenous delivery of drugs, is taking place at the Purdue University Center for Pharmaceutical Processing under sponsorship of the National Science Foundation (NSF) and a consortium of pharmaceutical companies. The project is directed by Professor Stanley Hem.

The role of the Microfluidizer processor is to supply large quantities of very small lipid droplets whose uniform size can be reproduced from trial to trial and study to study. Lipids are organic compounds (e.g., fats, oils, waxes, sterols, and triglycerides) that are insoluble in water but soluble in common organic solvents, are oily to the touch, and together with carbohydrates and proteins constitute the principal structural material of living cells. Since lipids dissolve inside cells, but not in a carrying medium, such as water, they make convenient containers in which to carry other compounds, such as drugs, into the body.

The small size of the lipid droplets produced by the Microfluidizer processor makes it possible to inject them into the blood without risking blockage of small blood vessels. The reproducibility of uniform particles allows scientists to benchmark their progress as they change other variables of the study. And, finally, the speed and ease-of-use of the Microfluidizer processor allow scientists to create the quantities of lipid droplets they need to move the research forward quickly.

“When I was in pharmacy school,” says Dr. Hem, “they told us we could only inject solutions into the blood — that you couldn’t inject suspension because the particles would clog up the capillaries and lead to thrombosis, and you couldn’t inject emulsions into the blood because the droplets would also plug up the capillaries.

“Now, with the Microfluidizer processor, you can make emulsions whose droplet size is much smaller than the diameter of the capillaries, and therefore it is safe to administer the drug intravenously.”

### A Great Number of Lives Have Been Saved

“The first application was for patients who needed intravenous feeding.” The solution was 5% dextrose. Sugars have calories but, surprisingly, not a lot of them. And so the 5% dextrose provided about 20 kilo calories per 100 ML That’s really not enough for a person to live on. Fats have a lot more calories than sugar. Once drug companies found they could make small oil droplets with the Microfluidizer processor, they were able to make 20% lipid emulsions that would not cause any thrombosis. A 100 ml solution of 20% lipid emulsion has 200 kilo calories, so the patient receives 10 times as many calories per volume. That makes a huge difference in their recovery. A great number of lives have been saved.”



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It was this success that prompted a number of drug companies to work with Purdue through this special NSF Center. “In the case of a lot of the newer cancer drugs,” say Hem, “we have big problems in giving them orally because they cannot be absorbed across the GI tract. But it seemed very promising to prepare them in the intravenous lipid emulsions and administer them that way.”

Once again, the Microfluidizer processor was key. “Right in the beginning before I did any lab work,” states Hem, “I realized the Microfluidizer processor would be the critical piece of equipment.” He uses the Model 110Y benchtop model. “The machine has worked flawlessly. It has allowed us to consistently achieve droplet sizes well below 1 micron. Emulsions prepared using ultrasound, the best method to produce small droplets prior to the development of the Microfluidizer processor, wouldn’t be safe to inject intravenously because you get substantial numbers of droplets larger than one micron. Furthermore, we can make an emulsion today with the recipe that we used a year and a half ago, and we still get the same droplet size that we got then. It’s wonderful.”

But having a reliable supply of submicron lipid droplets was only the prerequisite of Hem’s research, not the objective. The problem for the drug companies was that the lipids needed to be autoclaved prior to injection into a patient. That autoclaving — heating to 121 degrees C for 20 minutes — caused the droplets to coalesce back into larger droplets. The mission of the Purdue study was to find a way to prevent the droplets from coalescing during autoclaving. Now, near the end of a two-year effort, the objective of that mission is in sight. Hem’s solution was to cover the droplets in an envelope that protected them from coalescing. That envelope consisted of a surfactant (surface active agent) that set up a barrier layer at the interface between the droplet and surrounding water.

“I think we will finish up in another four months and publish our work. People will see it’s possible to achieve smaller changes in droplet sizes with autoclaving than now occur. What we’re doing is increasing the safety margin. Because of the lower risk of thrombosis, some drugs that were administered orally will now be administered intravenously, and drugs that were administered intravenously will be now administered with less risk to the patient. This will open up whole new drug therapies.

“This project wasn’t about the Microfluidizer processor,” Hem says. “But without the Microfluidizer processor there to give us the droplet sizes we needed, we would not be where we are today.”

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