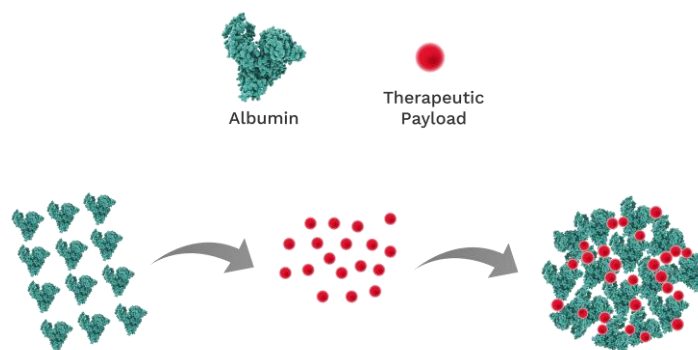


# Application Note



## Microfluidizer® Technology for Nanoparticle Albumin Bound (nab) Drug Delivery



### INTRODUCTION

Cancer treatments have been advancing in recent decades. Chemotherapy being one of the most widely adopted treatments. However, delivering these chemotherapeutics continues to be a major challenge, due to their high toxicity, low aqueous solubility and poor bioavailability. In addition, traditionally used solubilizing and delivery vehicles such as Cremophor EL and ethanol are also cytotoxic and can lead to severe allergic reactions.

Nanoparticle albumin bound (nab) technology is a novel, and one of the most attractive, platforms. Albumin is a natural and abundant protein occurring in plasma, which means it is not only biocompatible and biodegradable, but also non-toxic or immunogenic.

Abraxane® (Nab-paclitaxel) was the first FDA approved, highly successful, chemotherapy drug based on this nab-technology.

This Application Notes explores how creating stable nanoemulsions enables this drug to be successful.

## Microfluidizer® Technology for nab paclitaxel drug delivery

### THE CHALLENGE

Abraxane® is used to treat advanced cancer of the pancreas & breast cancers that have spread, along with non small lung cancer.

The natural properties of albumin as a blood transporter makes it an ideal vehicle for delivering therapeutic agents to targeted tumor sites. Human serum albumin (HSA) delivers the cancer chemotherapeutic (in this case paclitaxel) to the tumor site via several different pathways where the drug blocks the growth of the cancer, by preventing the cancer cells dividing and causing them to eventually die.

The challenge here is bringing together the paclitaxel and albumin and converting them into a suitable form, since simply mix the two together won't work.

Like many chemotherapeutics, Abraxane® is administered to patients via intravenous infusion, which means it has to be a sterile product. Filter sterilization is usually the preferred sterilizing method. For Abraxane® this requires achieving a mean particle size of 130 nanometers and a tight distribution.

This particle size and distribution also plays an important role during subsequent process steps such as solvent removal and lyophilization.

Choosing the right technology is a key step in ensuring the successful creation of the nab-particles.

### THE PROCESS

A preferable methodology for formulating nab-nanoparticles is via emulsification. The active ingredient, paclitaxel, is dissolved in an organic solvent to form an oil phase. This is mixed with an aqueous phase – an albumin solution - to create a coarse emulsion which is then emulsified using high shear. This shear is delivered with Microfluidizer® technology, which can achieve the desired droplet size and distribution. The resulting emulsion undergoes solvent removal, sterilization and lyophilization steps to create the final product in the form of powder.

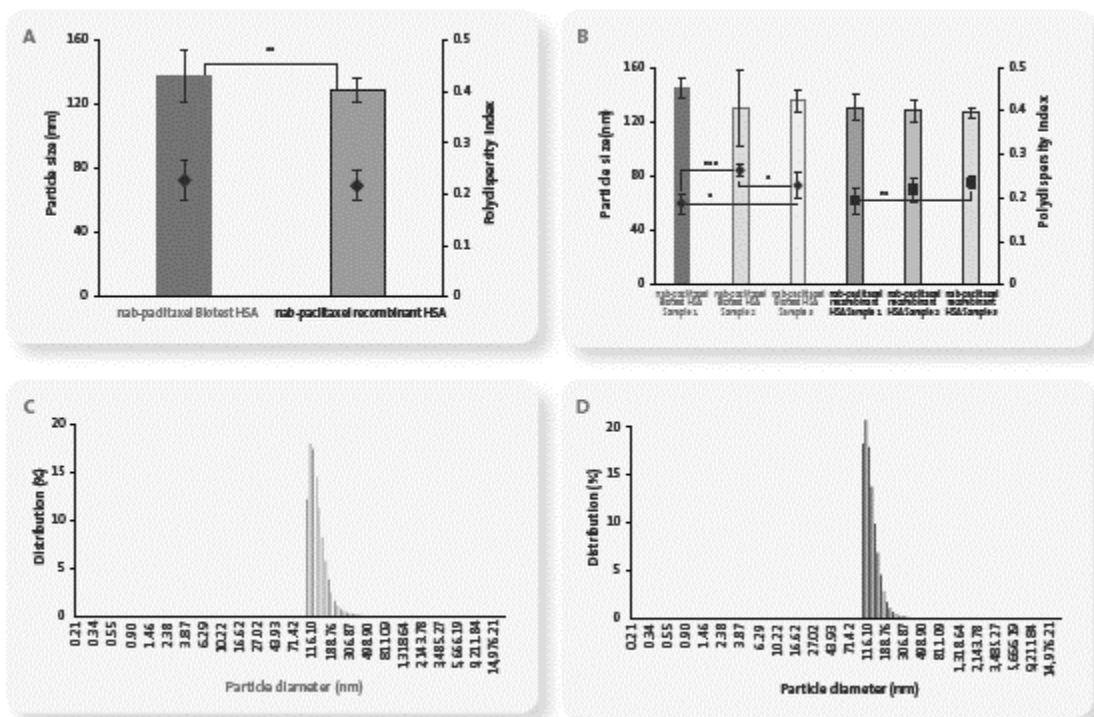
### Human Serum in Nab-technology -A Case Study

In this study, the preparation, processing and properties of nanoparticle nab-paclitaxel was evaluated after utilizing a LM20 Microfluidizer® processor.

The prepared nanoparticles displayed a narrow polydispersity index (PDI) and an approximate 130-140nm size range, therefore providing a suitable process for the reproductive preparation of nab-paclitaxel. Both processed materials exhibited zeta potentials of moderate colloidal stability indicating almost equal performance across different formulations. The materials also produced about 98% paclitaxel encapsulation efficiency and about 9% paclitaxel loading, resulting in desired similar characteristics.

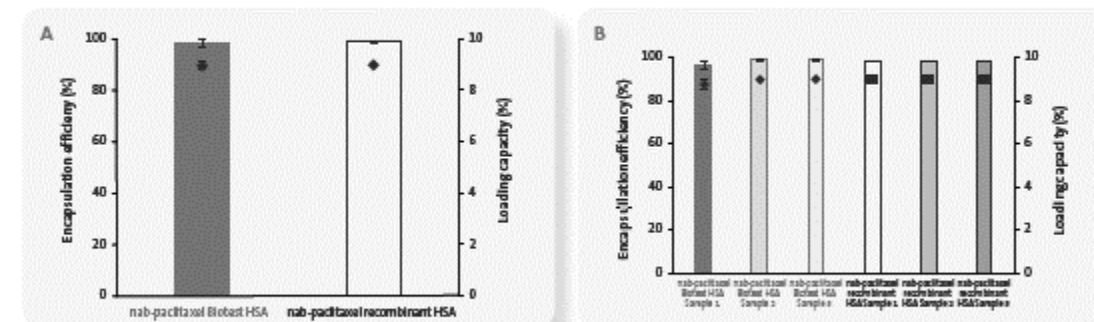
## Microfluidizer® Technology for nab paclitaxel drug delivery

### Particle Size and Particle Size Distribution



A Particle size (nm; primary y-axis; bar chart) and polydispersity index (secondary y-axis; dot chart) of nab-paclitaxel Biotech HSA in comparison to nab-paclitaxel recombinant HSA. B Particle size (nm; primary y-axis; bar chart) and polydispersity index (secondary y-axis; dot chart) of nab-paclitaxel Biotech HSA samples 1-3 and nab-paclitaxel recombinant HSA samples 1-3. C Representative particle size distribution histogram of nab-paclitaxel Biotech HSA. D Representative particle size distribution histogram of nab-paclitaxel recombinant HSA. Significant differences are marked as \*, \*\*, and \*\*\* which correspond to a p-value  $\leq 0.05$ ,  $0.01$  or  $0.001$ .

### Encapsulation Efficiency and Loading Capacity



A Encapsulation efficiency (primary y-axis; bar chart) and loading capacity (secondary y-axis; dot chart) of nab-paclitaxel Biotech HSA in comparison to nab-paclitaxel recombinant HSA. B Encapsulation efficiency (primary y-axis; bar chart) and loading capacity (secondary y-axis; dot chart) of nab-paclitaxel Biotech HSA samples 1-3 and nab-paclitaxel recombinant HSA samples 1-3. A and B: No significant differences were observed.

## Microfluidizer® Technology for nab paclitaxel drug delivery

### SCALABILITY

All results are directly scalable so the results in the lab are replicated in production. Results can be directly transferred from the R&D lab to the factory with full confidence because each model uses the same fixed geometry Interaction Chamber™.

These are multiplied when scaling up model by model. No matter what volume is processed, the results are consistent.

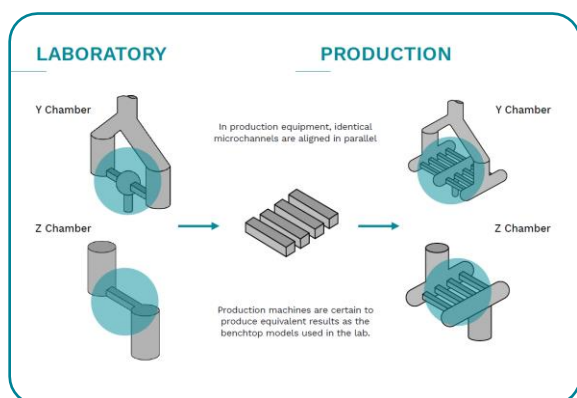


Figure 1 – shows how the chambers are configured for scale up

### THE BENEFITS

Microfluidizer® technology is ideal for creating nab-nanoparticles. With a proven track record of creating best-in-class nanoemulsions, this technology can:

- create desired droplet sizes with narrow particle size distribution
- achieve consistent results to ensure batch to batch repeatability
- enable easier down-stream, e.g., sterile filtration, processes

Microfluidizer® processors also significantly out-perform conventional high-pressure homogenizers (HPH) in producing effective nanoemulsions. Our data repeatedly shows that the Microfluidizer® processor is much more efficient in producing more uniform nanoemulsions when compared to HPH. Whilst also consuming much less energy than HPH.

Microfluidizer® processors are also:

- easy to operate
- reliable with low maintenance cost
- linearly scalable from 2ml to Liters per hour
- compliant with cGMP regulations