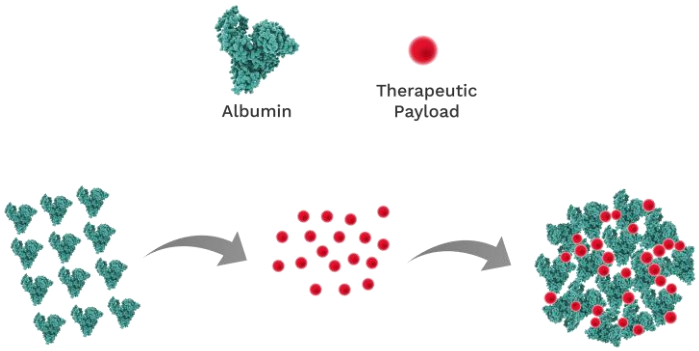
Microfluidics™

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[1-6]. 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[2,4,6].

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

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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[4].

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 a water-immiscible 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.

A Case Study

In this study, both plasma-derived HSA (pdHSA, provided by Biotest AG) and recombinant HSA (rHSA) were used to formulate nab-paclitaxel. A benchtop LM20 Microfluidizer® processor was used to process the formulation as explained above.

The prepared nanoparticle nab-paclitaxel was analyzed for various physical-chemical properties including particle size, particle size distribution, zeta potential, and encapsulation efficiency. The prepared nanoparticles displayed an approximate 130-140 nm particle size range with narrow polydispersity index (PdI) as shown in Table 1 and Figure 1, and zeta potentials of moderate colloidal stability (Figure 2) for both HSA sources, all of which were comparable to the commercially available product (Abraxane®)[1-2,4]. Both formulations also achieved very high paclitaxel encapsulation efficiency (~98%) and drug loading (~9%).

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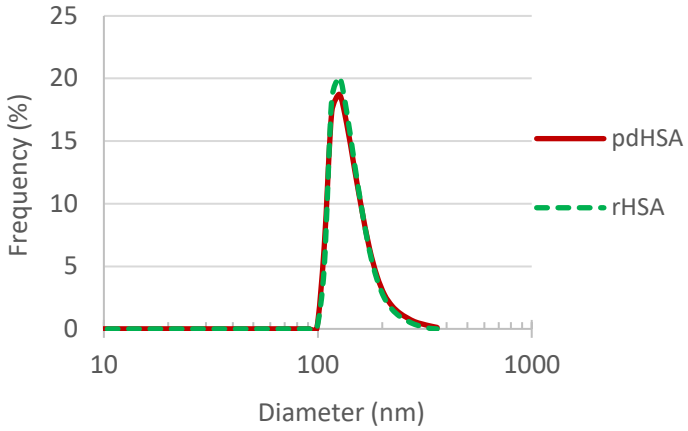

Figure 1. Particle size distribution of nab-paclitaxel formulated with pdHSA and rHDA

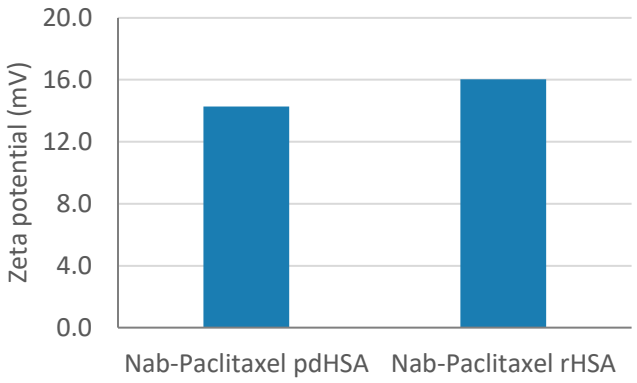

Figure 2. Surface charge of nab-paclitaxel formulated with pdHSA and rHDA

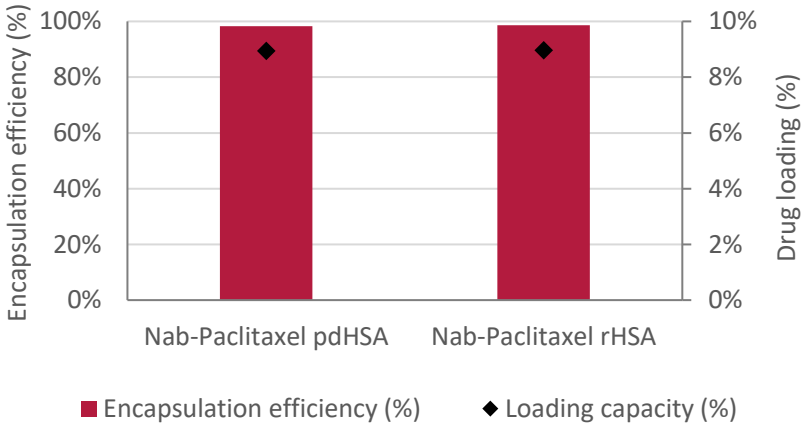

Figure 3. Drug encapsulation and loading of nab-paclitaxel formulated with pdHSA and rHDA

Table 1. Particle size and PdI of nab-paclitaxel formulated with pdHSA and rHDA

Formulation	Z-Average Size	PDI
nab-Paclitaxel (pdHSA)	129.18	0.208
nab-Paclitaxel (rHSA)	134.97	0.215

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REFERENCE

1. M.R. Green, etc., Ann. Oncol., 2006, 17(8): 1263-1268.
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3. J. Iglesias, Breast Cancer Res., 2009, 11 (Suppl 1), S21.
4. N. Desai, AAPS J., 2012, 14: 282-295.
5. R.D. Luca, etc., Onco. Targets Ther., 2019, 12: 1621-1627.
6. M. S. Hassan, etc., Biomedicines, 2023, 11(7).

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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.

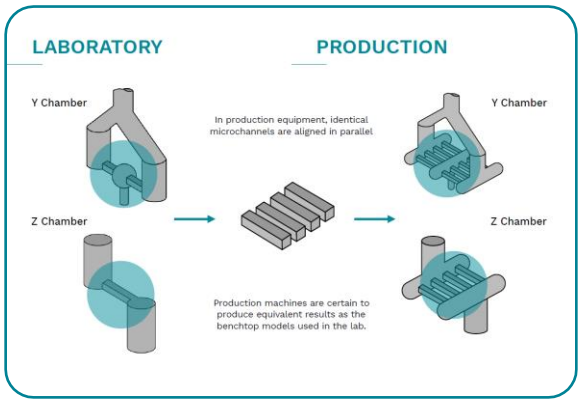

Figure 1 – shows how the chambers are configured for scale up

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