Progressing the Development of AZD2811 Nanoparticles for Intravenous Administration

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Project Background

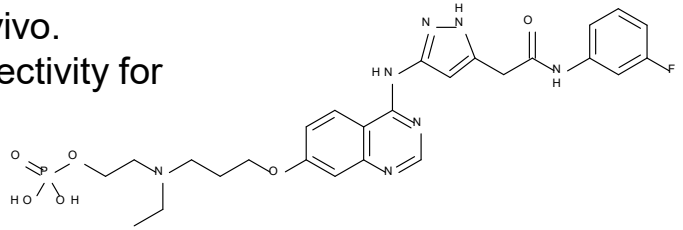
Product Development

- Target product profile and potential Critical Quality Attributes
- Formulation optimisation
- Developing a robust manufacturing process
- Biopharmaceutics and potentials CQAs

Summary

Overcoming the Limitation of AZD1152 using Drug Delivery

AZD1152, a phosphate pro-drug, rapidly converts into AZD2811 in-vivo.
AZD2811 is a selective AurB inhibitor with over 1000-fold higher selectivity for aurora kinase B over aurora kinase A[1]



AZD1152 (barasertib, phosphate pro-drug)

AZD1152 demonstrated positive Proof of Concept in AML.
Despite this, the program was stopped due to:

- The 7-day infusion regimen limited the indications to those where patients were already hospitalised
- The dose-limiting, mechanism-related bone marrow toxicity meant that efficacious doses could only be achieved in patients with haematological cancers

These clinical limitations may be overcome by having:

- A **slow release profile** where a single infusion gives multiple days efficacious cover in an outpatient setting
- An **improved efficacy** with the potential to establish efficacious doses in solid tumour settings

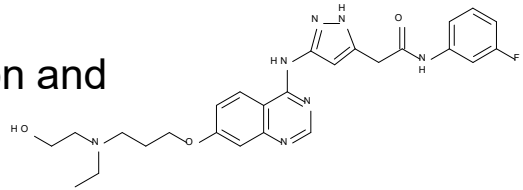
1. *Mortlock AA, Foote KM, Jung FH et al., Discovery, synthesis, and in vivo activity of a new class of pyrazoloquinazolines as selective inhibitors of aurora B kinase. J Med Chem, 2007 50(9):2213-24.*

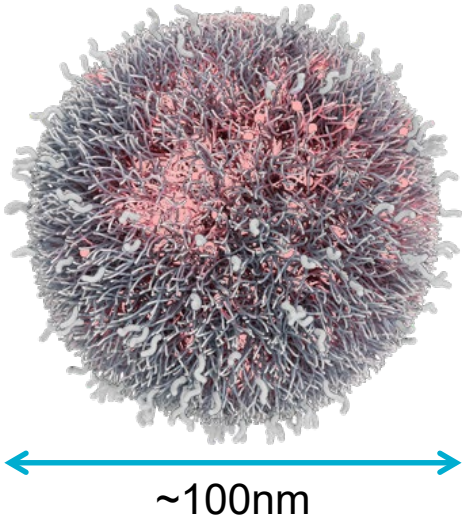
ACCURINS® Nanoparticles with Controlled Drug Release Rates

AZD2811 is encapsulated in a novel nanoparticle delivery system[1, 2, 3]

Drug release via diffusion

Hydrophobic ion pairing with an acidic counter ion aids encapsulation and slows drug release





Controlled-Release Polymer Matrix

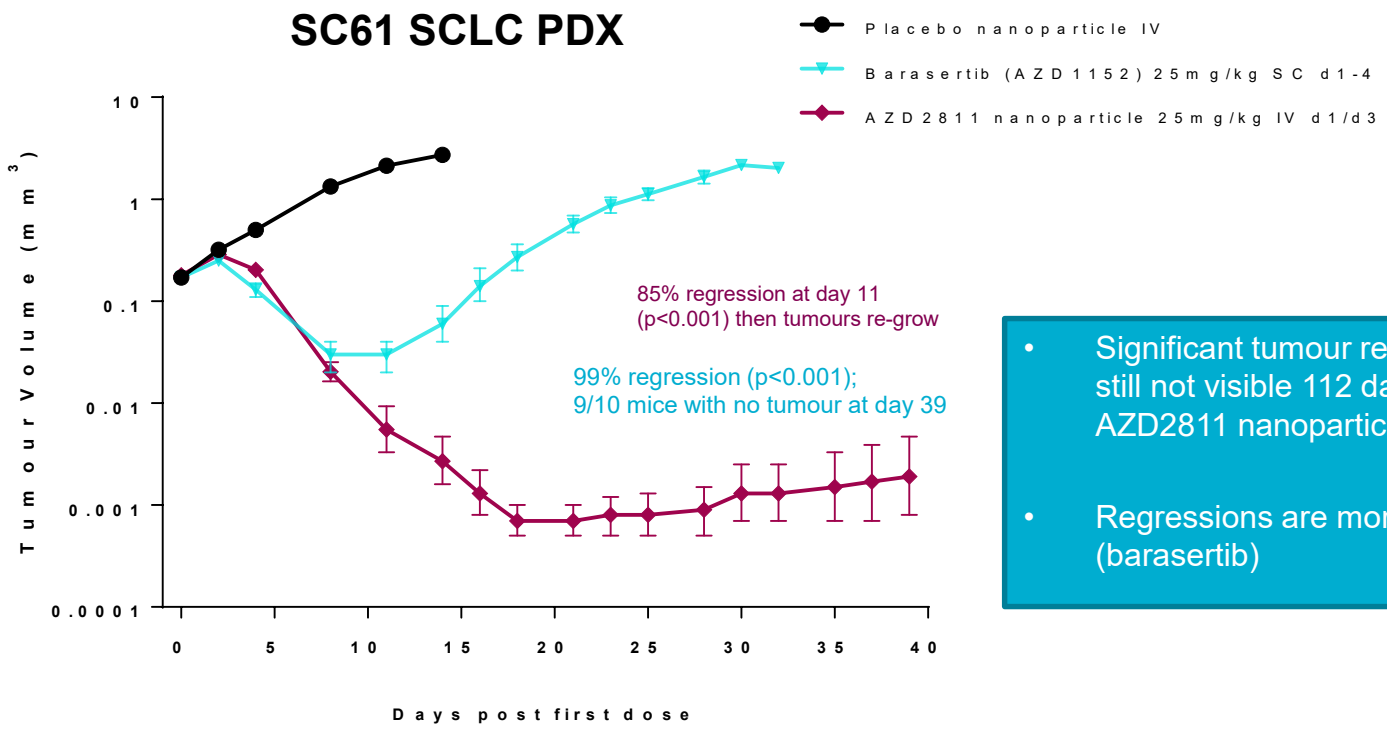
Polylactic acid (PLA)
- FDA approved polymer
- Non-covalently entraps payload
- Regulated release of payload over days

Stealth and Protective Layer

PEG
- Hydration shell
- Protects against immune detection
- Long circulation time

References:
1. Young HS, Shin E, Wang H, Nolan J, Low S et al, A novel in situ hydrophobic ion pairing (HIP) formulation strategy for clinical product selection of a nanoparticle drug delivery system. J Control Release. 2016; 229:106-119.
2. Ashton S, Taylor P, Curtis N et al. AZD1152HQPA AccurinTM nanoparticles inhibit growth of diffuse large B-cell lymphomas and small cell lung cancer. Cancer Res. 2015; 75:3102.
3. Ashton S, Song YH, Nolan J, Cadogan E, Murray J et al., Aurora kinase inhibitor nanoparticles target tumors with favorable therapeutic index in vivo. Sci Transl Med 2016; 325ra17-325ra17.

AZD2811 nanoparticle shows improved efficacy over AZD1152 at equivalent dose intensity in SCLC models



- Significant tumour regression with >80% tumours still not visible 112 days after a single cycle of AZD2811 nanoparticle
- Regressions are more durable than AZD1152 (barasertib)

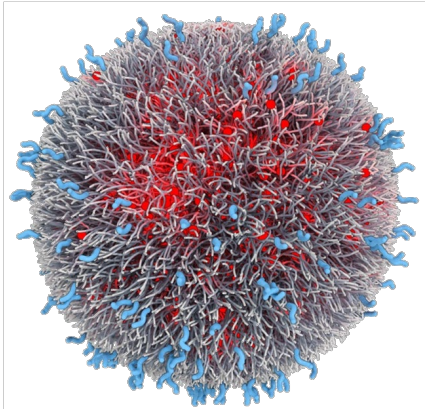
Ashton et al, AACR, 2017 - Development of AZD2811, an aurora kinase B inhibitor, incorporated into an Accurin™ nanoparticle for use in haematological and solid cancers

Nanoparticle Target Product Profile

Physical & Chemical Composition
Release-controlling Polymer
+/- targeting ligand
Drug loading
Counter-ion
Particle size distribution
Surface charge
Drug release rate

Production process
Process aids
Emulsion composition
Particle formation
Process controls (pressure, temp. etc)
Purification

Critical material attributes
Block architecture
PEG and PLA M_n
Homo-PLA, free PEG
Residual monomer, solvent



Size: ~100 ± 30 nm
Drug load ~ 15%
Similar in vitro
Release profile

Potential Critical Quality Attributes

- **Surface characteristics**
- **Drug Release rate/profile**
- **Particle size & PDI**
- **Morphology**
- **Free drug concentration**

Nanoparticle Properties impact the in vivo performance, both efficacy and safety

- Biodistribution – nanoparticle circulation time and clearance, localized accumulation
- Release and clearance of drug

Formulation optimization

Formulation Optimization of AZD2811 Nanoparticle

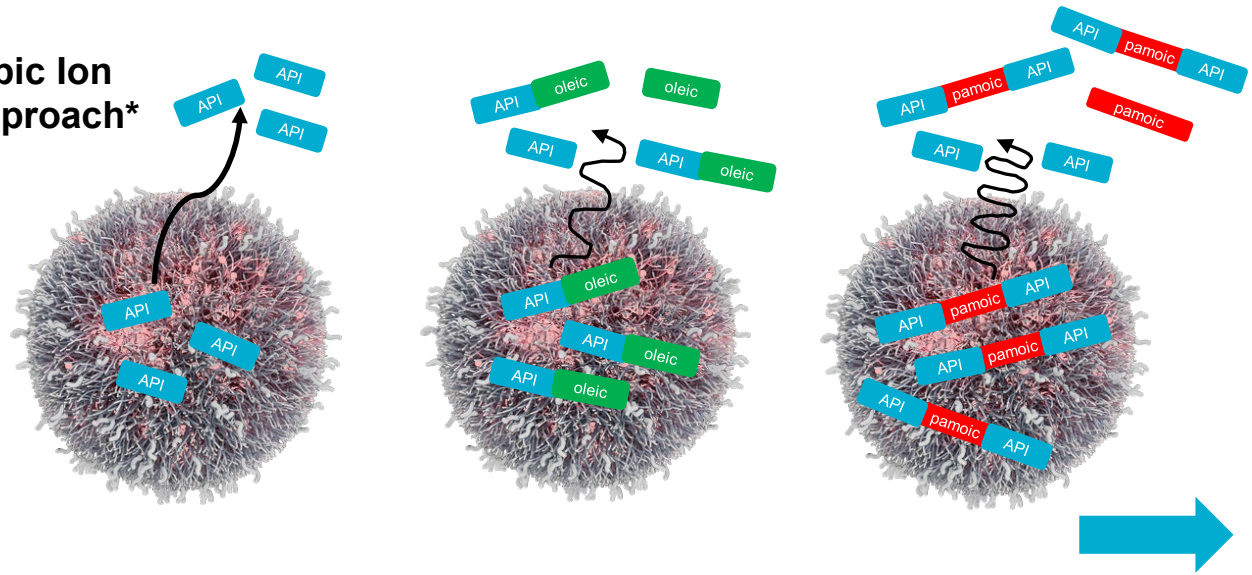
Goals

- To increase drug loading to > 12% while maintaining slow release rate
- Improve process efficiency

Benefits

- Reduced number of vials for patients
- Reduced excipient load
- Reduced development costs/cost of goods

Hydrophobic Ion Pairing Approach*



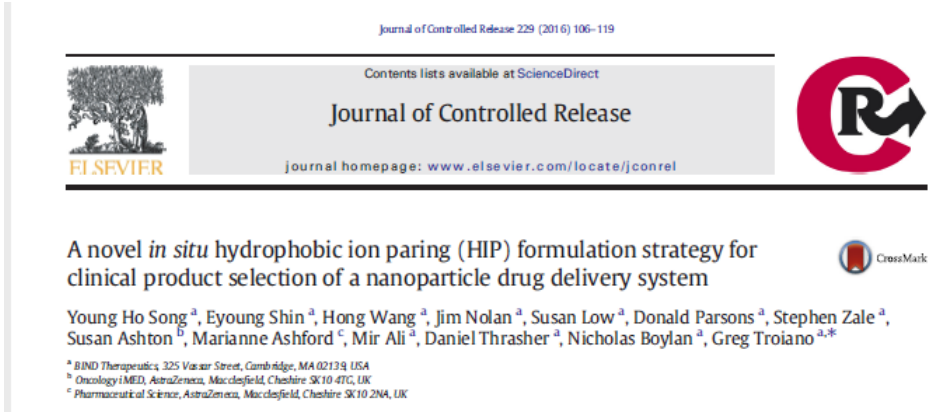
Drug loading	15%
Encapsulation Efficiency	71%
Time 50% release	120 hours

** Song et al, J Controlled Release, 2016, 229, 106*

AZD2811 Drug Formulation & Product

Main Components & Function of Nanoparticle

Component	Function
AZD2811	API (~20% nanoparticle)
PLA-PEG	Hydrophobic PLA (16kDa) to control release Hydrophilic PEG (5kDa) as stealth layer
Pamoic Acid	Functional excipient, forms hydrophobic ion pair with API AZD2811:Pamoic 1:0.5



Journal of Controlled Release 229 (2016) 106–119

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A novel *in situ* hydrophobic ion paring (HIP) formulation strategy for clinical product selection of a nanoparticle drug delivery system

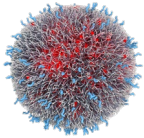
Young Ho Song [a], Eyoung Shin [a], Hong Wang [a], Jim Nolan [a], Susan Low [a], Donald Parsons [a], Stephen Zale [a], Susan Ashton [b], Marianne Ashford [c], Mir Ali [a], Daniel Thrasher [a], Nicholas Boylan [a], Greg Troiano [a,*]

[a] BIND Therapeutics, 325 Vassar Street, Cambridge, MA 02139, USA
[b] Oncology iMED, AstraZeneca, Macclesfield, Cheshire SK10 4TG, UK
[c] Pharmaceutical Science, AstraZeneca, Macclesfield, Cheshire SK10 2NA, UK

- Presented as a frozen suspension for Ph1 & 2
- Lyophile will be investigated for commercial product

Developing a robust manufacturing process

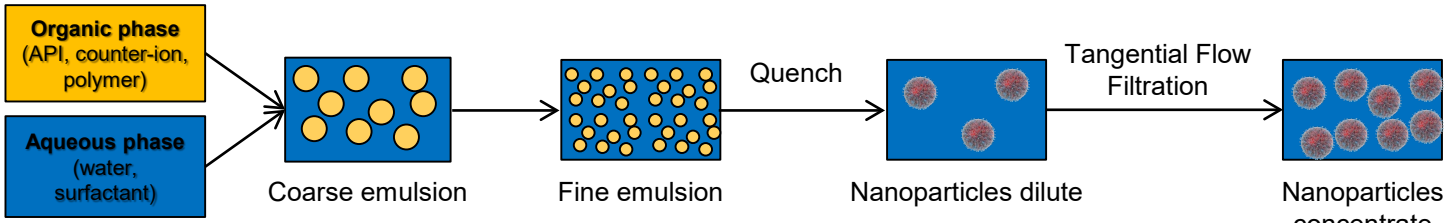
Manufacturing Process for AZD2811 nanoparticle



Target Attributes

Size: ~100 ± 30 nm **Drug Load: ~ 20%**

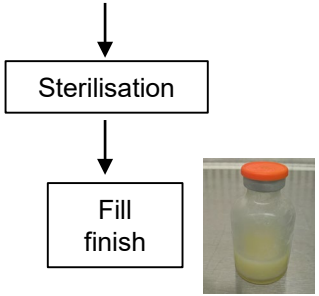
Similar *In vitro* release profile



$$d_{max} = \varepsilon^{-2/5}\ \gamma^{3/5}\ p^{-1/5}$$

Energy density — Surface tension — Laplace pressure

The shear stress applied by the process must exceed the Laplace pressure, which is inversely proportional to droplet diameter



Nanoparticle Manufacturing Process Control Aspects

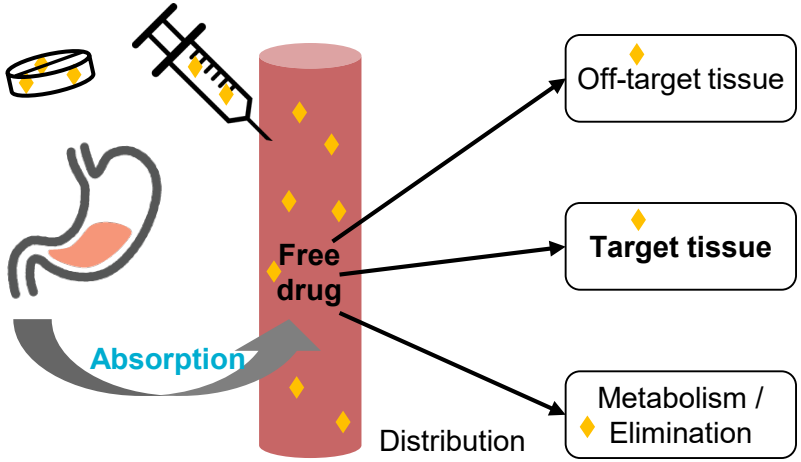
Process Step	Input Parameters	Key Outputs	Impact
Coarse Emulsification	Surfactant quantity Energy Temperature Phase viscosities	Droplet size distribution Emulsion stability	Increasing energy input → smaller droplets Decreasing surface tension (more surfactant) → smaller droplets Smaller droplets → Increased Laplace pressure Increasing temperature → less stable emulsion & bigger droplets
Fine Emulsification	Surfactant quantity Energy Temperature Phase viscosities	Droplet size distribution Emulsion stability Drug loading Drug release rate	Decreasing surface tension → smaller droplets Smaller droplets → Increased Laplace pressure Increasing temperature → less stable emulsion, reduced drug loading
Droplet stabilisation	Energy Time Sink conditions Temperature/ Pressure	Droplet size distribution Drug loading Drug release rate	Temperature / pressure affects residual solvents, drug loading Rate of solvent removal impacts drug loading, residual solvents
Clean & concentrate particles	Diavolumes Transmembrane pressure Flow rate Concentration	Free drug content Solvent content Drug loading Concentration / Assay	More diavolumes → reduced solvent / free drug concentration, longer processing times and waste Need to optimise transmembrane pressure, concentration, flow rate, temp & diavolumes

Biopharmaceutics and potential CQAs

Biopharmaceutics of AZD2811

Conventional dosage forms

ADME



- Efficacy/safety driven by systemic exposure = plasma conc profile of **free drug**

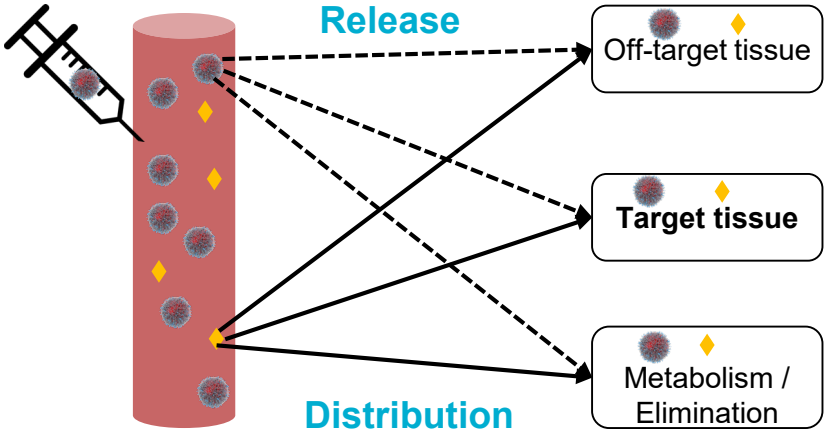
(target and off-target tissue concs in eqm with plasma conc)

- Plasma concentration limited by drug **absorption** (unless IV)

  ➔ **API solubility/permeability, drug product dissolution**

IV Nanomedicines

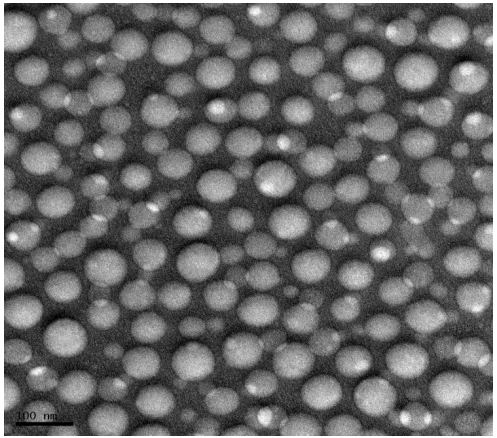
ADME

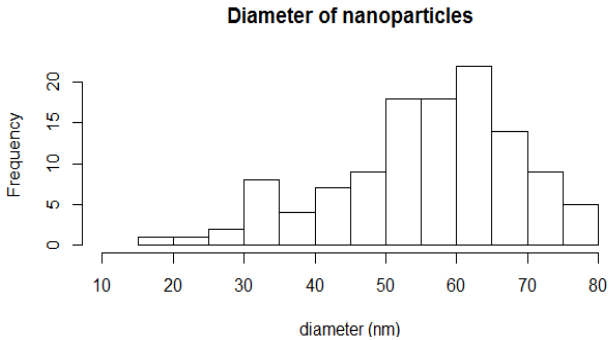


- Systemic exposure: 2 entities present **released drug AND encapsulated drug**
- Different distribution patterns ➔ target exposure no longer driven **only** by plasma conc ➔ **Focus on NP attributes that can impact release and distribution**

Particle Sizing of Nanoparticles

Particle size using Transmission Electron Microscope (TEM)





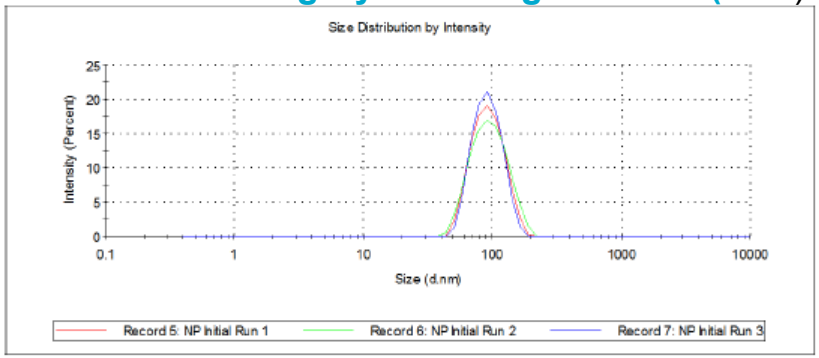
Mean: 57 nm

Standard deviation: 13 nm

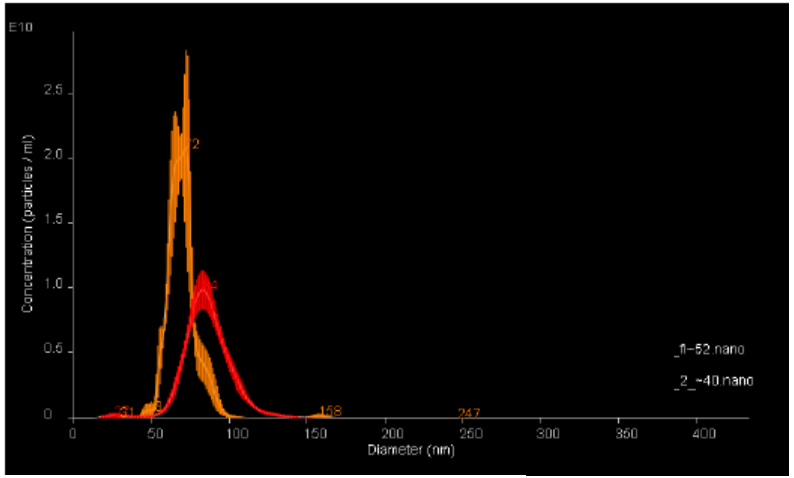
Range: 18 – 80 nm

Average size of nanoparticles (based on measurement of 118 nanoparticles):

Particle size using Dynamic Light Scatter(DLS)



Particle size using nanoparticle Tracking Analysis (NTA)

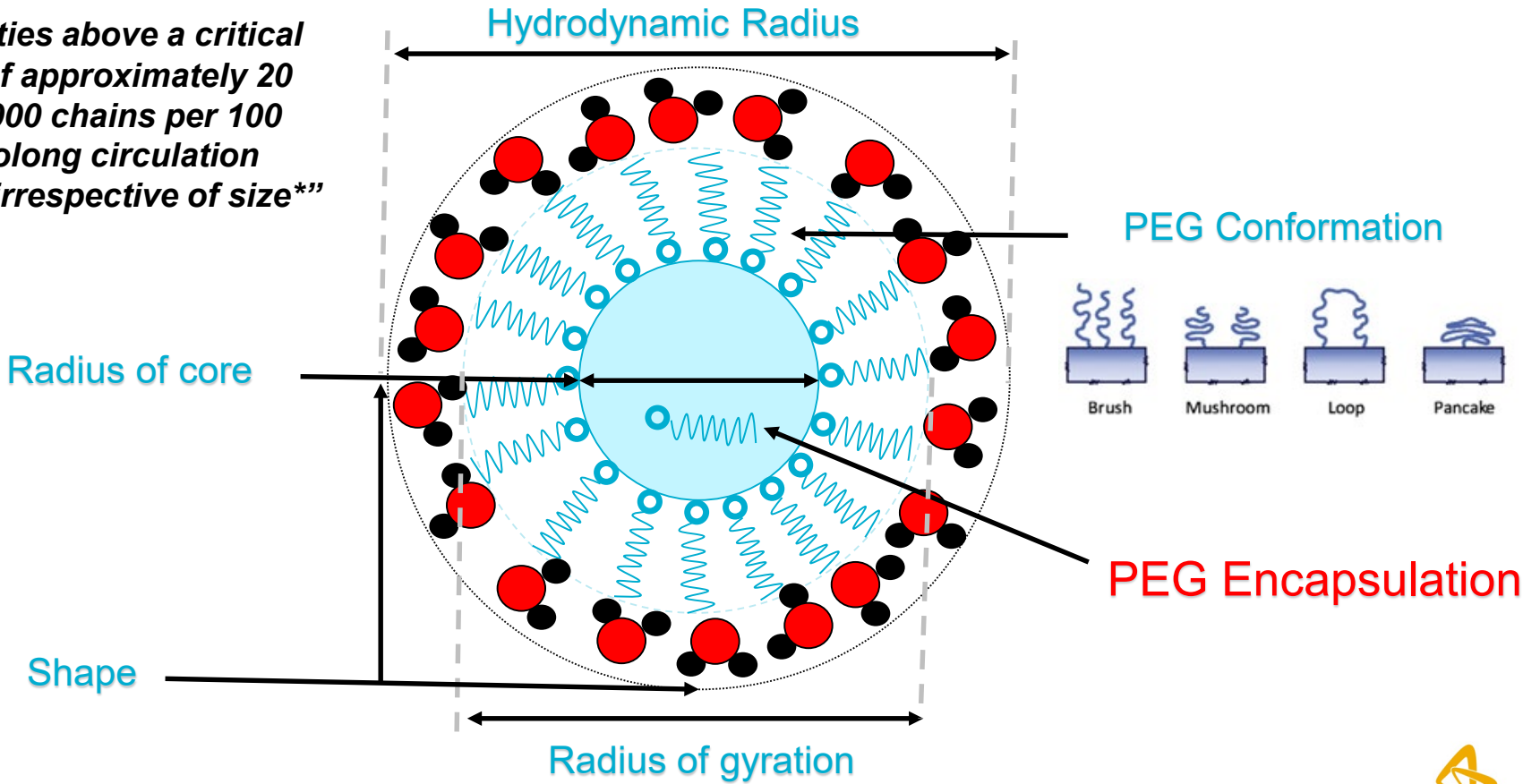


Scatter
Mode: 67.8 nm
Mean: 70.3 nm
Total concentration: $4.08X10^{11}$ particles/mL

Fluorescence:
Mode: 86.4 nm
Mean: 85.8 nm
Total concentration: $3.05X10^{11}$ particles/mL

Stealth Layer Analysis- Quality and In Vivo performance

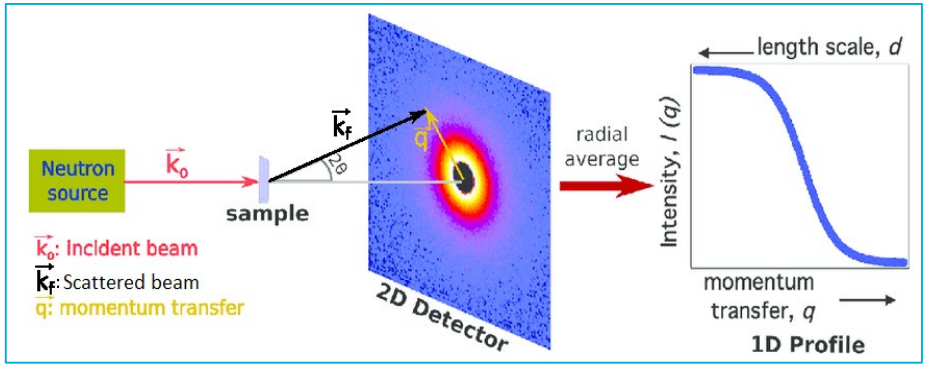
"Densities above a critical value of approximately 20 PEG-5000 chains per 100 nm^2 prolong circulation times, irrespective of size*"



*Bertrand et al, Mechanistic understanding of in vivo protein corona formation on polymeric nanoparticles and impact on pharmacokinetics, Nat. Comm, 2017, 8, 777

Stealth Layer Characterisation

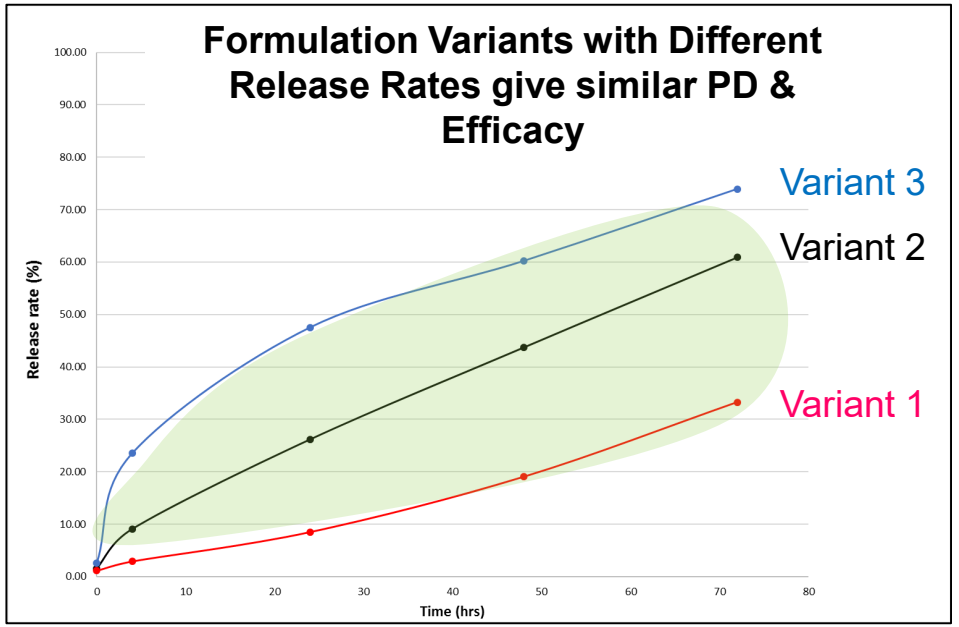
- Surface PEG quantification with NMR
  - Quantify total PEG in/on nanoparticle
  - Quantify PEG in nanoparticle
  - Subtraction = PEG on surface
- Determine size (R_g) via SANs and therefore surface area
- Packing density: PEG/ 100 nm^2



Neutron Scattering

Further work to support Product Development

- Identify CQAs and define acceptable drug product attribute ranges to ensure equivalent performance across clinical batches
- Define a robust, biorelevant, discriminatory IVR (in-vitro release) method and assess in-vitro in-vivo correlation
- Process scale up to commercial scale



In Summary

- AZD2811 is progressing through Phase I/II
- Significant progress in understanding the physical and chemical composition of the nanoparticles
- Robust clinical product manufacturing process
- Sound understanding of process parameters that will aid commercial process optimisation
- Further work on-going to optimise the in-vitro in-vivo release correlation for product commercialisation

Acknowledgements

- Many many colleagues working in the nanomedicines field in AstraZeneca Pharmaceutical Sciences, Oncology and Pharmaceutical Technology and Development groups

- AZD2811 Project Team and sub teams

- External collaborators in particular those from ex BIND Therapeutics, University of Warwick and ISIS.