

NanoSolution® case study: Using nano milling to improve dissolution rate of abiraterone acetate

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aptyspharma 
THE FORMULATION COMPANY®

4th Losan Drug Delivery Conference, Binzen

Feb.15th 2022

APTYS PHARMA*CEUTICALS*



Development of its own products

- Loramyc ®
- Testocream ®
- Metapain ®



APTYS PHARMA*SERVICES*



CRO in pharmaceutical R&D

- Preformulation
 - **SoluDiag ®**
 - **NanoSolution ®**
- Design of complex formulations
- Analytical development
- Quality control and stability studies

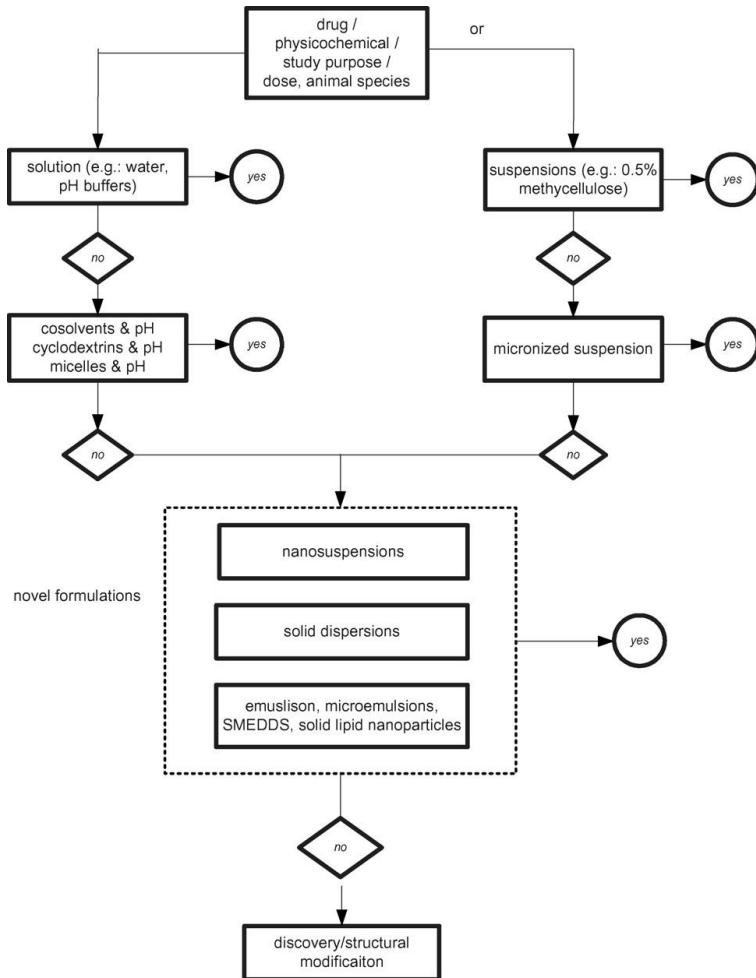


World Health Organization

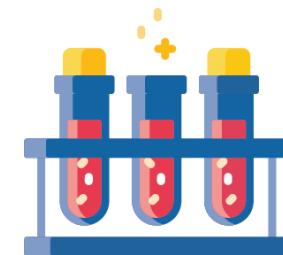


WHY SOLUDIAG® AND NANOSOLUTION ®?

- *≈ 40% of NCE are poorly soluble.*
- *Biotech companies have little amount of substance available*



SoluDiag ®



NanoSolution ®



Source : Developing early formulations : Practice and perspective : Ping Li, Luwei Zha
– International journal of Pharmaceutics 341 (2007)



A step by step process to assess solubility and formulate poorly soluble substances

E Explore

solubility of the candidate in about 20 different conditions of solvents and co-solvents

S Select

few conditions using a more elaborate technique

C Confirm

the best condition using state of the art methods

Advantages:



Low amount of product (100-1000mg)



Fast process



Cost effective



Solvents compatible with pre-clinical or clinical applications



Essential for formulation design



A one step process to find the best conditions to obtain nanosized poorly soluble substances



Dual centrifugation (n=40)



Nanoparticles with potentially

- higher solubility
- higher bioavailability
- lower food effect

Advantages

Low amount of product
(100-1000mg)



Fast process



Cost effective

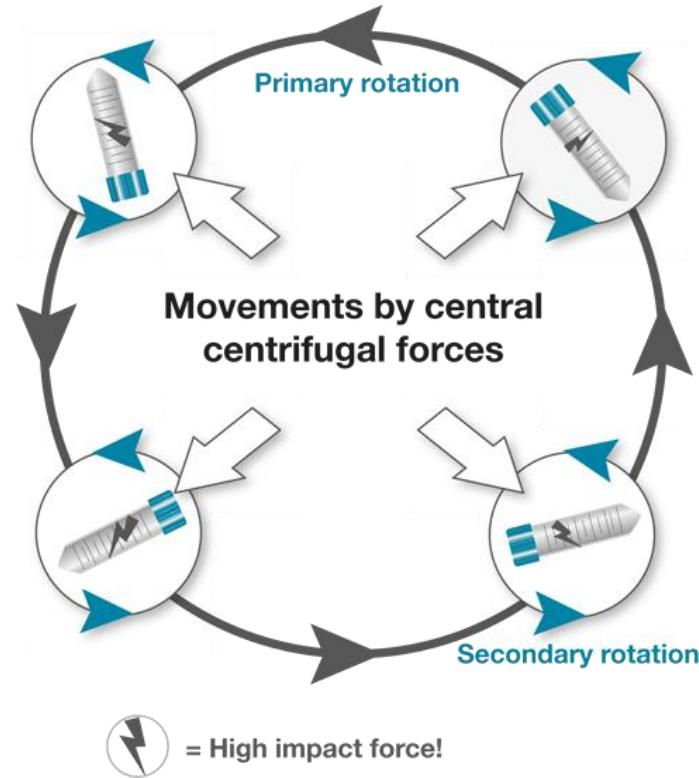


Ideal for DOE in the frame
of QbD



Essential for formulation
design

Dual Centrifugation(Zentrilmix 380R Hettich)



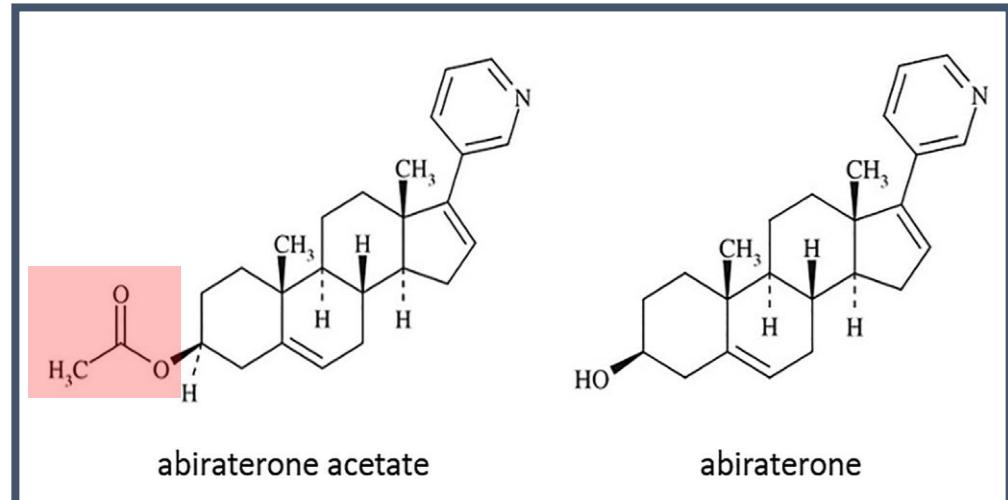
NanoSolution® case study: Using nano-milling to improve dissolution rate of abiraterone acetate

A study in partnership with



Abiraterone acetate (ABA)

- *Inactive prodrug of abiraterone*
- *Indication : prostate cancer*
- *BCS class IV*
- *Solubility: < 1 µg/ml*
- *Log P: 5.19 (very hydrophobic leading to a **strong positive food effect**)*



- Two products on the market :



Janssen

and generics



What's the difference between Yonsa® and Zytiga®?



Zytiga®
(abiraterone acetate)
250 mg, 500 mg tablets



Particle size (D50)

3 to 10µm

0.1 to 1.2µm

Recommended dose

1,000 mg
(2x500 mg tablets or 4x250 mg
tablets) with **prednisone**

500 mg
(4x 125 mg tablets)
with **methylprednisolone**

Food effect

YES

NO



Application of dual centrifugation screening to reduce particle size of ABA

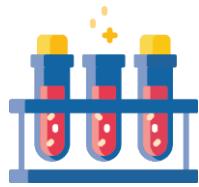
Objectives

- **To find composition** allowing a particle size reduction : $100 < D_{50} < 150 \text{ nm}$
- To check **robustness**
- To check **repeatability**
- To check **stability**
- To analyse in **vitro/in vivo release**



Application of dual centrifugation screening to reduce particle size of ABA

Methods



1mL suspensions of ABA containing different polymers and surfactants and 0.35mm diameter ZY-P ceramic beads (SiLibeads®, Sigmund Lindler)



Nanomilling using dual centrifugation, 1500 rpm, 90min, 4°C (Zentrimix 380R, Hettich)



Particle size analysis using laser diffraction particle size analyzer (Mastersizer 2000, Hydro 2000SM Malvern)



Application of dual centrifugation screening to reduce particle size of ABA

Variable parameters

Parameter		Percentage					
Polymer	HPMC 3mPas	1	2	3	3.5	4	5
	PVP-VA64	1		2		5	
	Poloxamer 188	1		2		5	
Surfactant	Docusate			0.1			
	Polysorbat 80		0.1		0.5		
Abiraterone acetate			10		20		

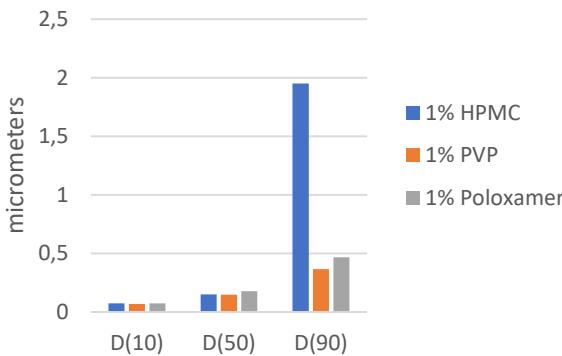
Polymers and surfactants allow stabilization by steric stabilization and ionic repulsion



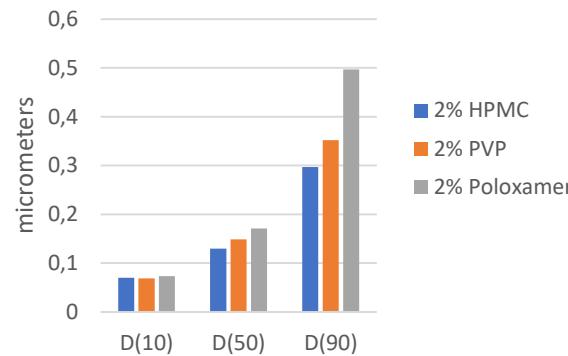
1st screening results:

Effect of polymer type

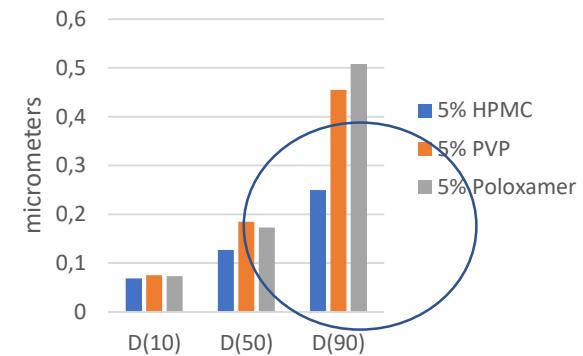
1% polymer, 0.1% docusate



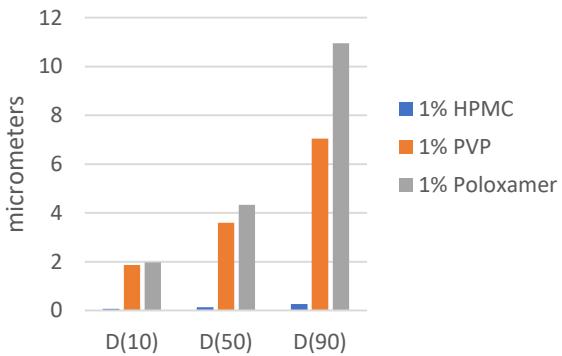
2% polymer, 0.1% docusate



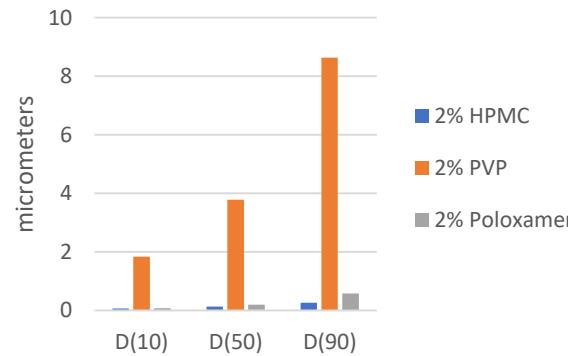
5% polymer, 0.1% docusate



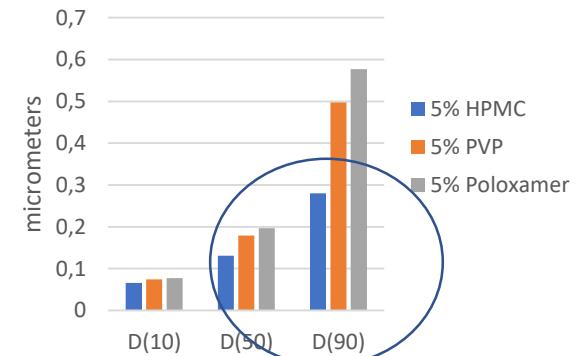
1% polymer, 0.5% polysorbate



2% polymer, 0.5% polysorbate



5% polymer, 0.5% polysorbate



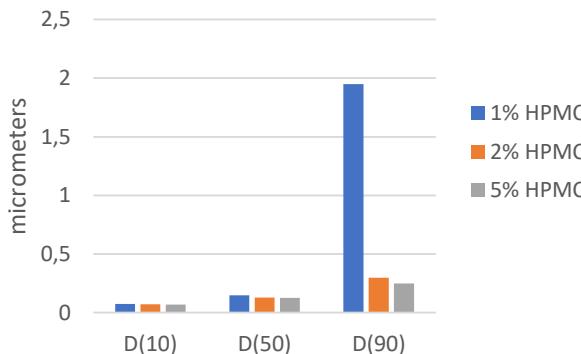
➤ Best results with HPMC



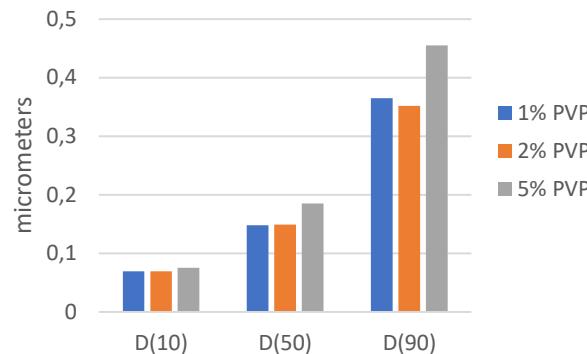
1st screening results:

Effect of polymer concentration

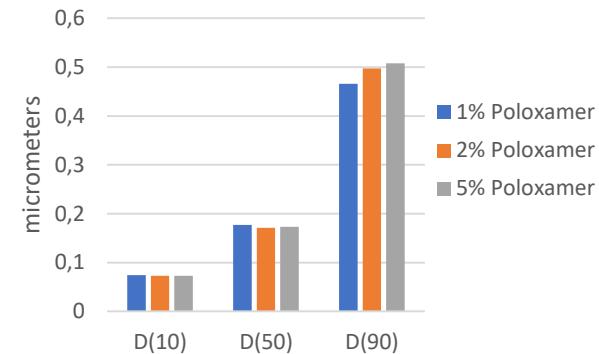
HPMC (0.1% docusate)



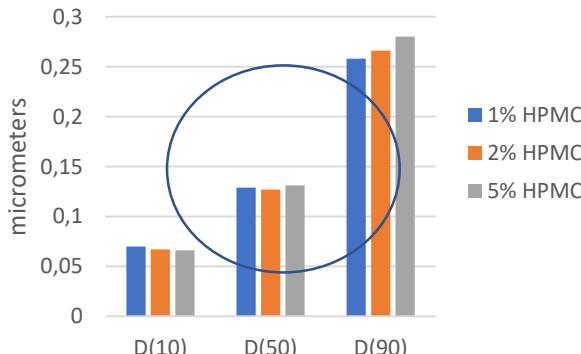
PVP (0.1% docusate)



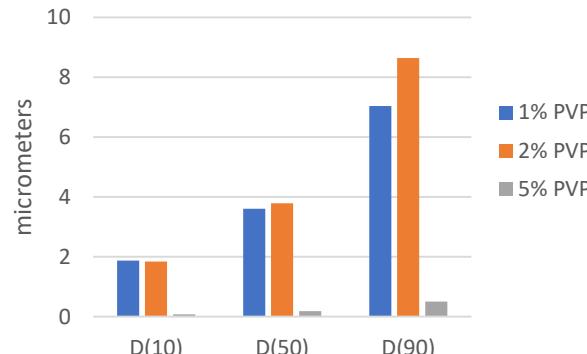
Poloxamer (0.1% docusate)



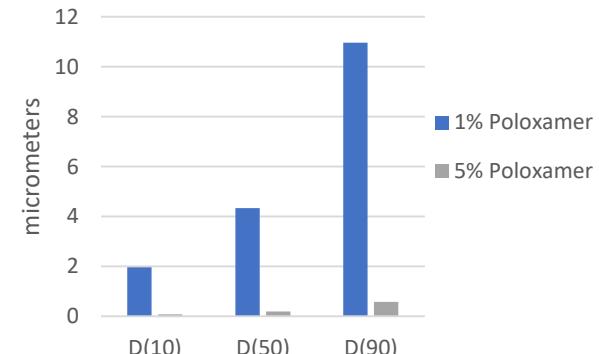
HPMC (0.5% polysorbate)



PVP (0.5% polysorbate)



Poloxamer (0.5% polysorbate)

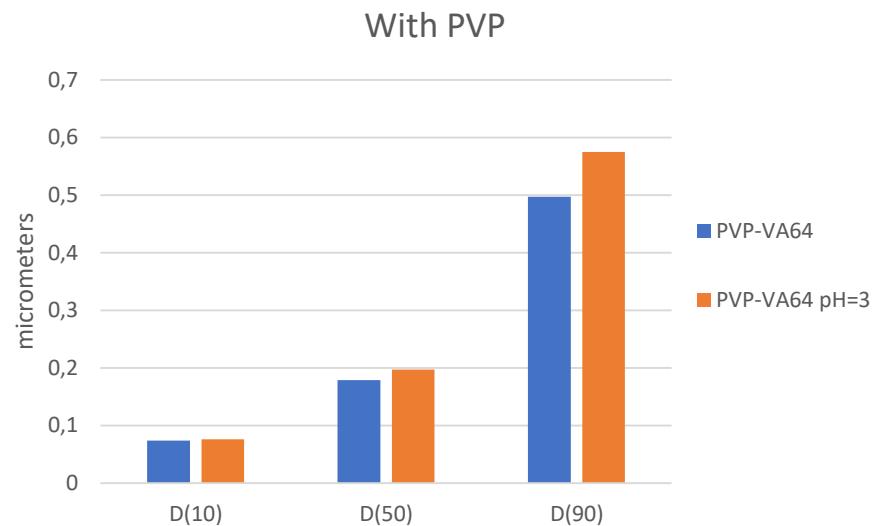
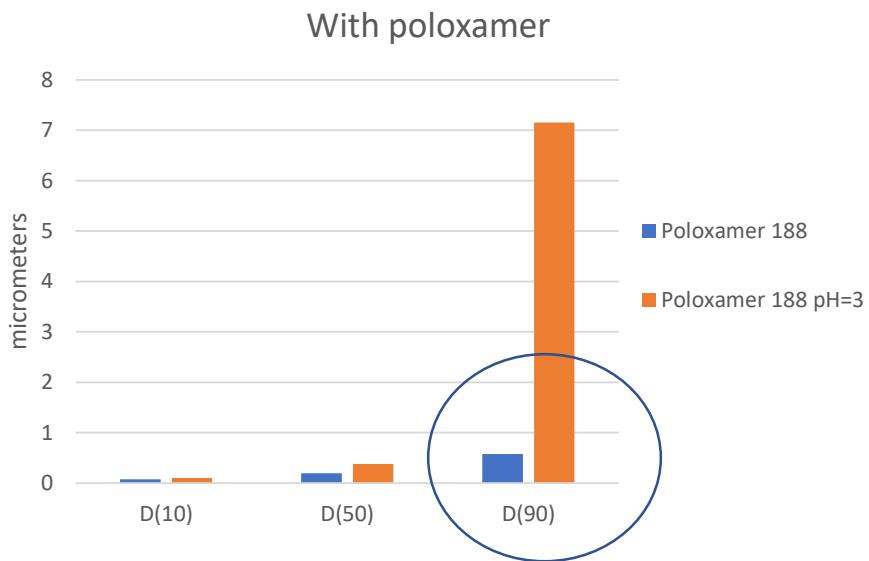


➤ No effect of concentration with HPMC



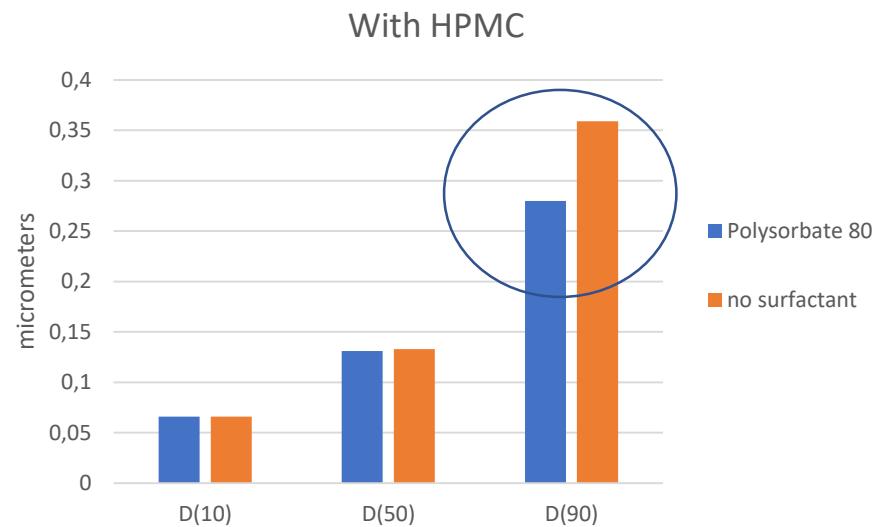
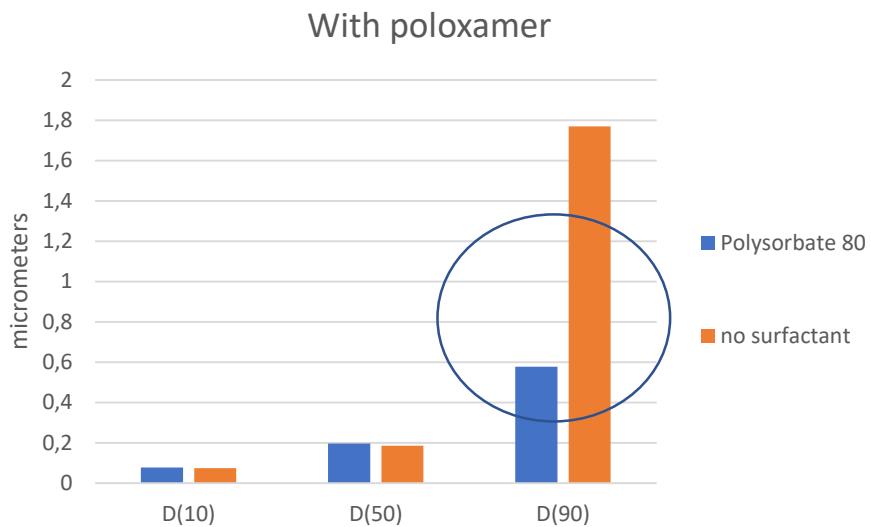
1st screening results:

Effect of pH



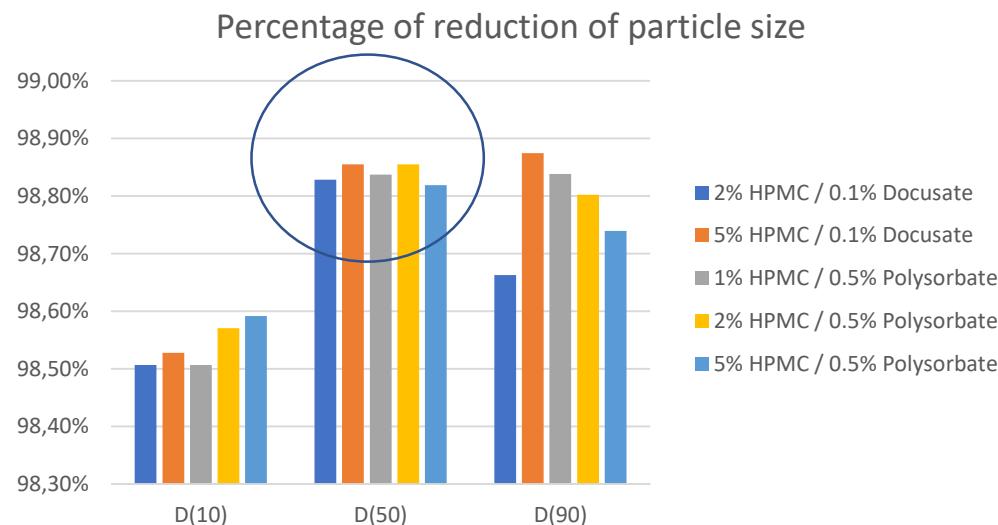
1st screening results:

Effect of surfactant



1st screening results:**Best results with HPMC**

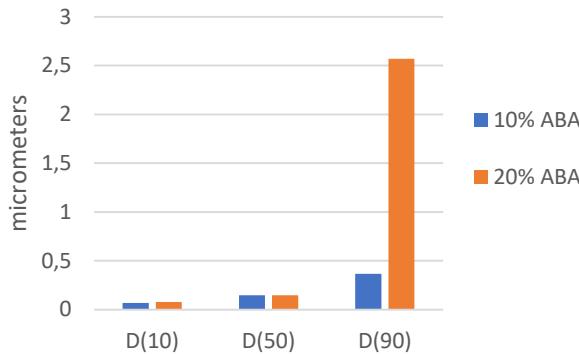
SAMPLE	ABA %	Polymer	%	Surfactant	%	D(10)	D(50)	D(90)
Control	10	-	-	Polysorbate 80	0.5	4.687	11.092	22.207
4	10	HPMC 3 mPas	2.0	Docusate	0.1	0.070	0.130	0.297
7	10	HPMC 3 mPas	5.0	Docusate	0.1	0.069	0.127	0.250
10	10	HPMC 3 mPas	1.0	Polysorbate 80	0.5	0.070	0.129	0.258
13	10	HPMC 3 mPas	2.0	Polysorbate 80	0.5	0.067	0.127	0.266
16	10	HPMC 3 mPas	5.0	Polysorbate 80	0.5	0.066	0.131	0.280



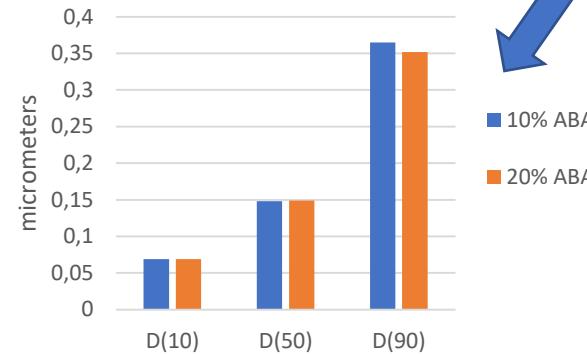
2nd screening results:

Robustness, effect of percentage of ABA

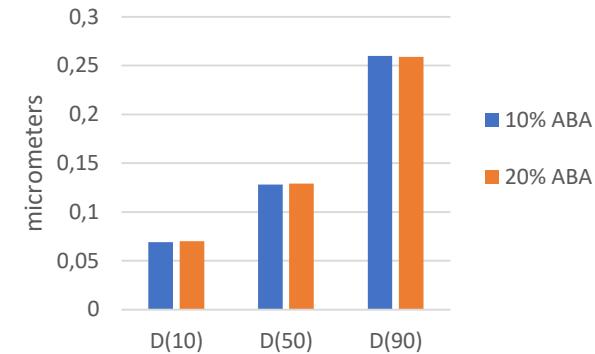
2% HPMC, 0.1% Docusate



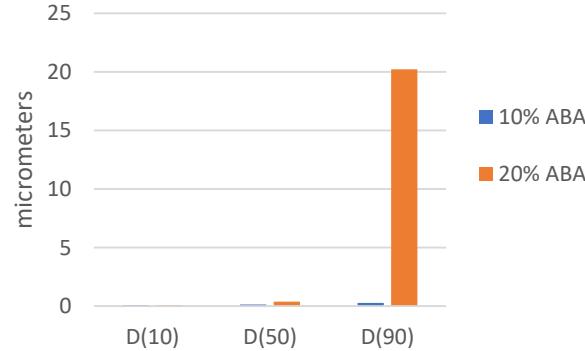
1% HPMC, 0.5% Docusate



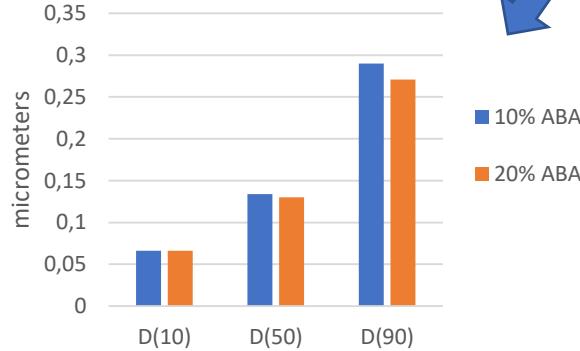
5% HPMC, 0.5% Polysorbate



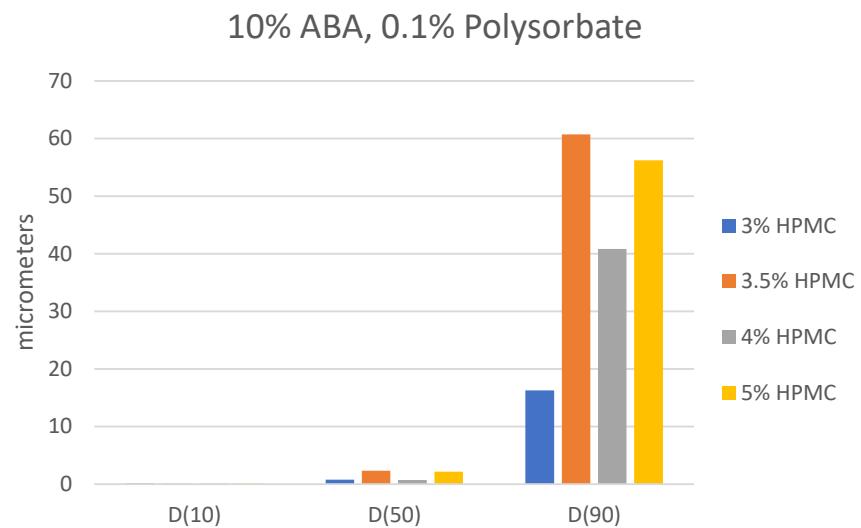
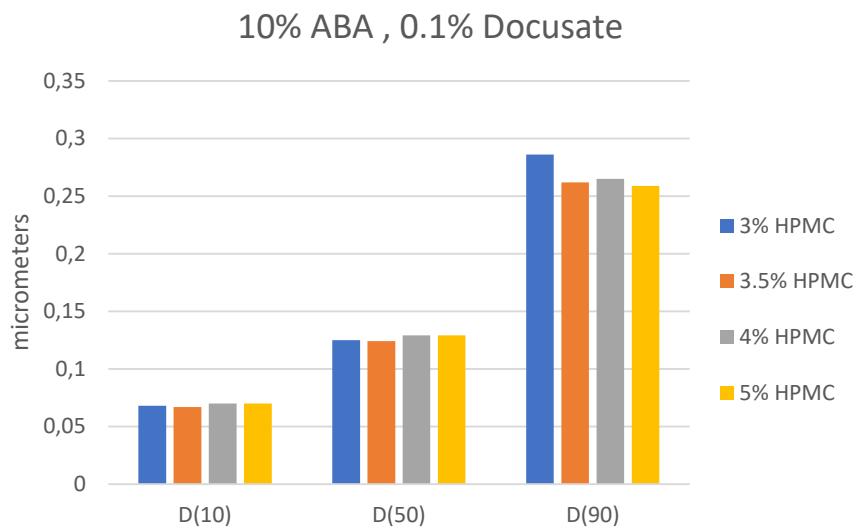
2% HPMC, 0.5% Polysorbate



5% HPMC, 0.5% Polysorbate

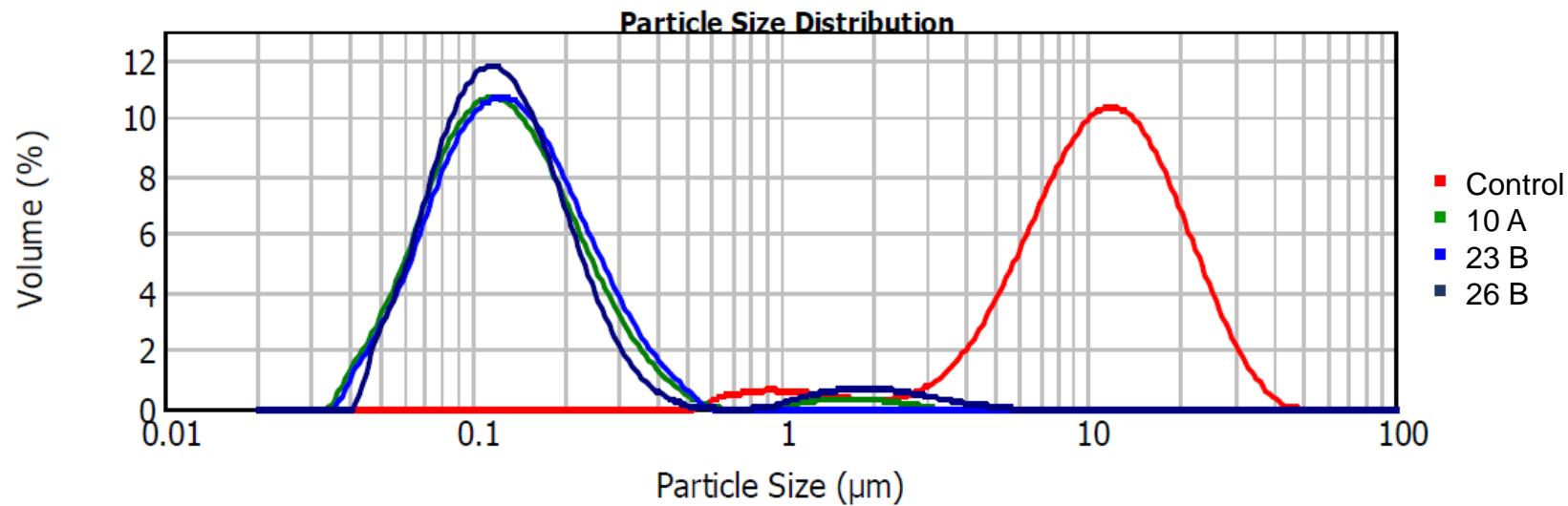


3rd screening results: **effect of surfactant and HPMC,**

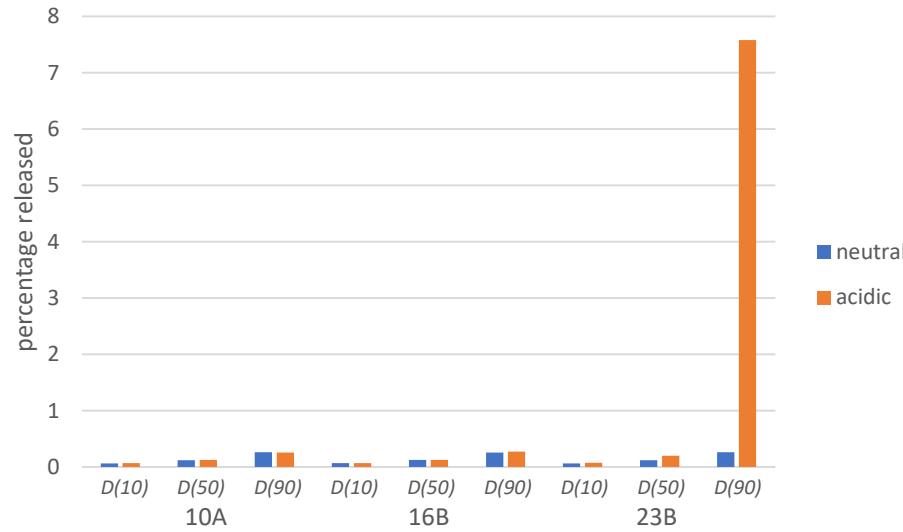


Selected compositions for further analysis

COMPOSITION	ABA	HPMC	POLYSORBATE	DOCUSATE
10A	10%	1%	0.5%	-
16B	20%	5%	0.5%	-
23B	20%	3.5%	-	0.1%



**Assessment of the effect of acidic environment on the granulometry of nanonized abiraterone
(HCl pH2 37°C, 1h)**



COMPOSITION	ABA	HPMC	POLYSORBATE	DOCUSATE
10A	10%	1%	0.5%	-
16B	20%	5%	0.5%	-
23B	20%	3.5%	-	0.1%



IN VITRO STUDIES

Solubility of ABA in pH4.5 buffer according to SDS concentration

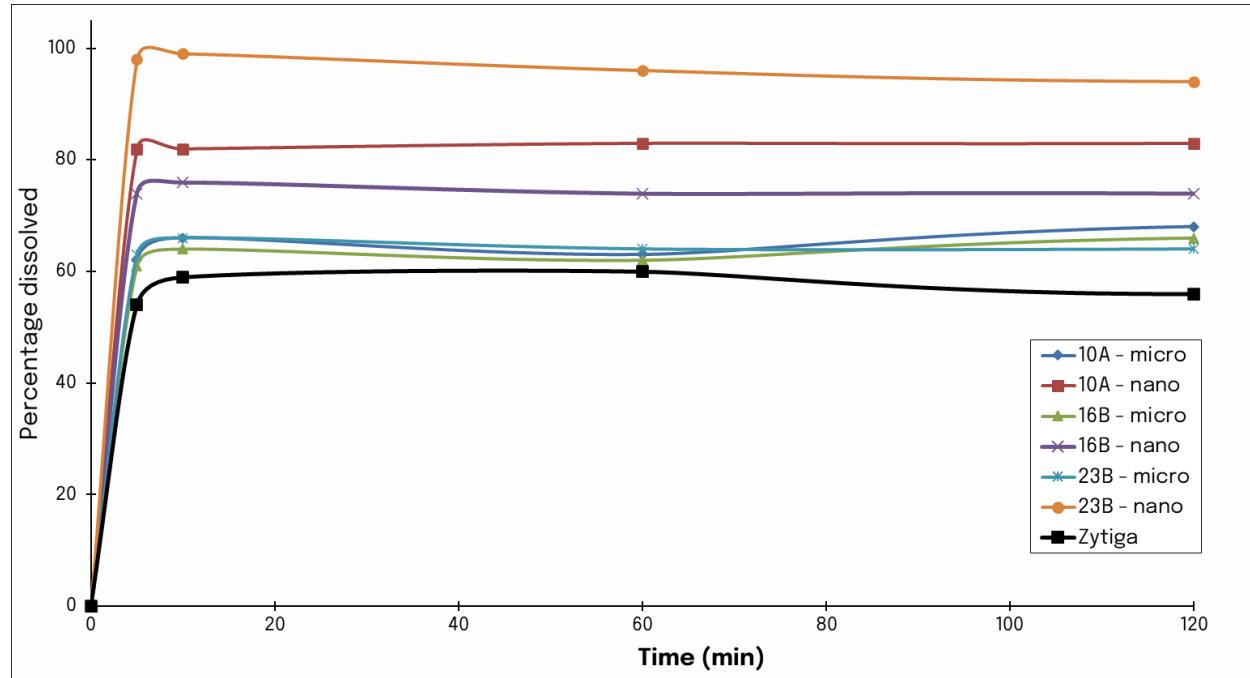
SDS (%)	AbA ($\mu\text{g/mL}$)
0.025	4
0.05	67
0.1	340

Experimental conditions

IN VITRO DISSOLUTION SETTINGS	
Equipment	Dissolution tester AT7 SOTAX®
Apparatus	Paddle USP2
Dissolution medium	Buffer pH 4.5 with 0.05% SDS
Initial volume (ml)	500
Dissolution temperature	37°C ± 0.5°C
Stirrer rate (rpm)	50
Analysis concentration	0.2 mg/ml
Sample addition	1 ml for 100mg/ml suspension 0.5 ml for 200mg/ml suspension
Sampling method	0.1 μm filter

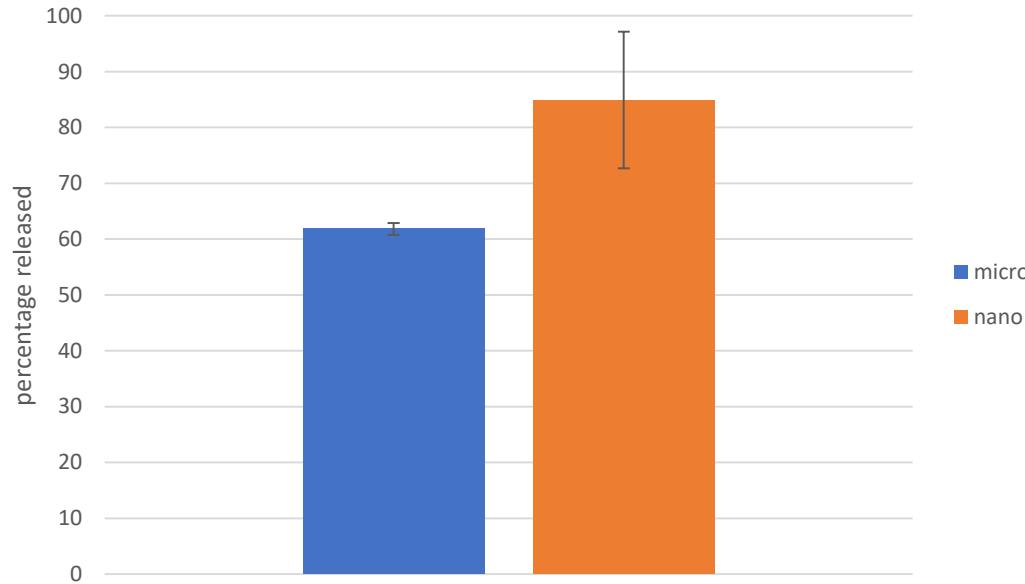


IN VITRO STUDIES



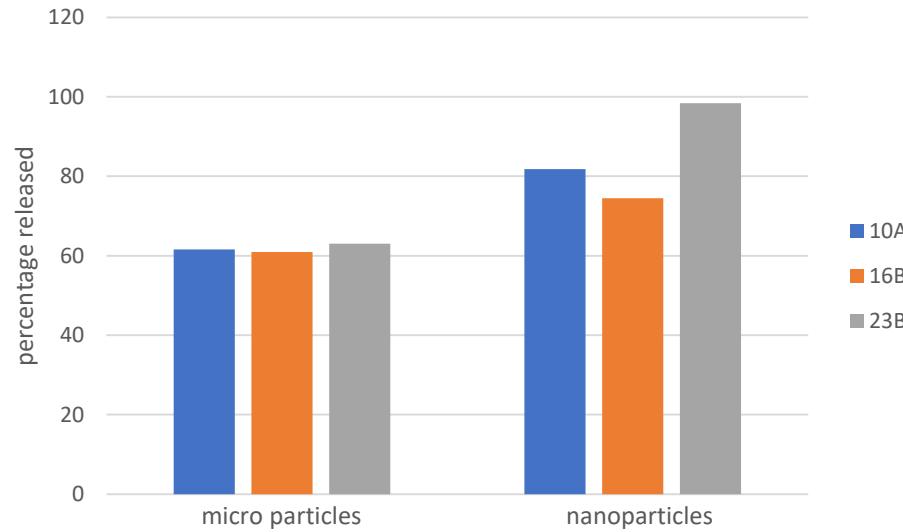
IN VITRO STUDIES

Effect of particle size at 5 min



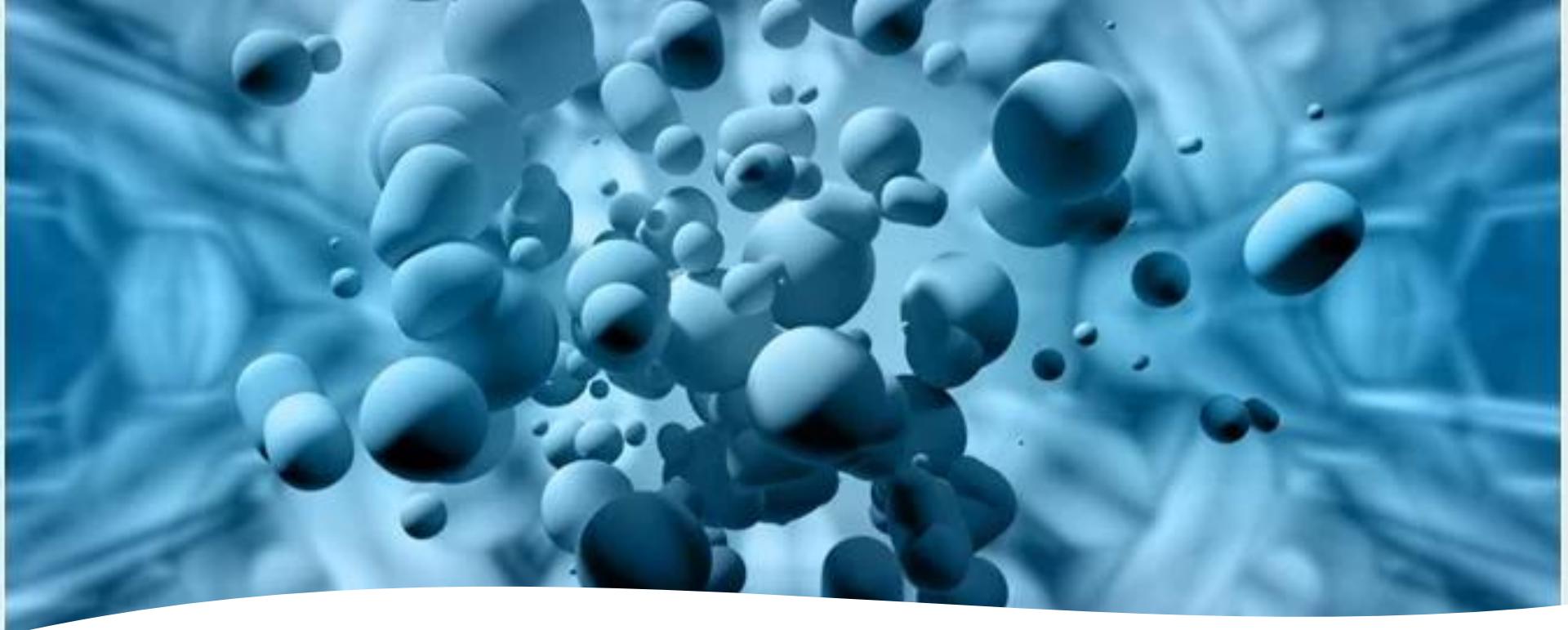
IN VITRO STUDIES

Effect of composition at 5 min



COMPOSITION	ABA	HPMC	POLYSORBATE	DOCUSATE
10A	10%	1%	0.5%	-
16B	20%	5%	0.5%	-
23B	20%	3.5%	-	0.1%





CONCLUSION

- We have shown that NanoSolution® is a straightforward way to screen many conditions with **few materials** and within a **short period of time**
- We have shown that nano milling **improves solubilization** of abiraterone acetate
- The best results were obtained with **HPMC as polymer**
- The best results were obtained with **docusate as surfactant** but stability in acidic conditions was not good
- Interestingly, our data with native (not nanonized) and nanonized ABA are **similar to the characteristics of Zytiga® and Yonsa®** respectively



NEXT STEPS

- **In vivo study in rats** : compare bioavailability of the best nano suspension with the not treated abiraterone
- **Zetapotentiel and powder diffraction (XRPD)** of the nanosuspension
- **Lyophilisation** of nanosuspension and **manufacturing of tablets** with the selected nanosuspension and **in vitro comparison with Zytiga®**
- **Stability study** at $5^{\circ}\text{C} \pm 3^{\circ}\text{C}$ on 4 and 8 weeks





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Thank you for your attention



aptyspharma®

THE FORMULATION COMPANY®