UNIVERSITÀ DEL PIEMONTE ORIENTALE

Case study: Sviluppo formulativo di una sospensione orale estemporanea di un farmaco poco solubile

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Nanonized itraconazole powders for extemporary oral suspensions: Role of formulation components studied by a mixture design

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AIMS:

- to prepare a dried product containing a high amount of ITZ in form of nanocrystals and able to promptly re-form a nanosuspension in contact with water
- to model ITZ particle diameter as a function of system composition
- to investigate the role played by the excipients on the comminution of ITZ particles and on the re-dispersibility of dried nanosystem in water

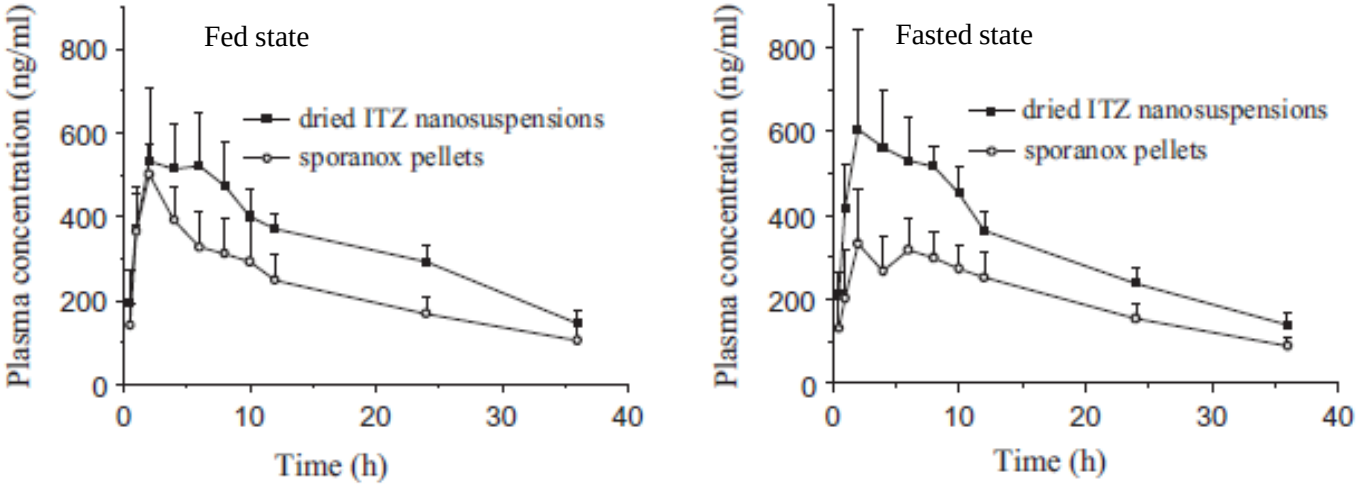
Itraconazole (ITZ)

a very poor soluble drug (<1ng mL^{-1} at pH 7.0)

Marketed oral dosage form: granules (ITZ, sugar, cellulose polymer, surfactant) obtained by layering techniques (Sporanox®)

Alternative oral dosage form: nano-crystals (ITZ, stabiling polymer, surfactant, sugar) obtained by top-down (size reduction) or bottom-up (precipitation) processes

Nanosuspension (precipitation + spray drying)
ITZ:HPMC:mannitol (1:0.5:2)
dose = 15 mg Kg^{-1}; n = 6 (rats)



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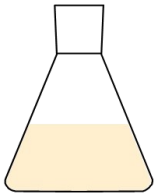
Composition of mixture

itraconazole (ITZ)
polysorbate 20 (TW20)
hydroxypropylmethylcellulose - HPMC (E5)

Process

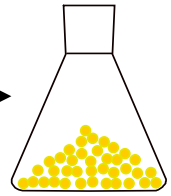


ITZ+TW20 in water

1200 bar/30′; 25 °C

+HPMC E5

temperature =160 °C
air flux = 742 L h^{-1}
Ø nozzle = 0.6 mm
feeding rate = 4 mL min^{-1}



dried nanosuspension

Experimental design

Mixture Design

for systems whose properties are functionally related to the composition

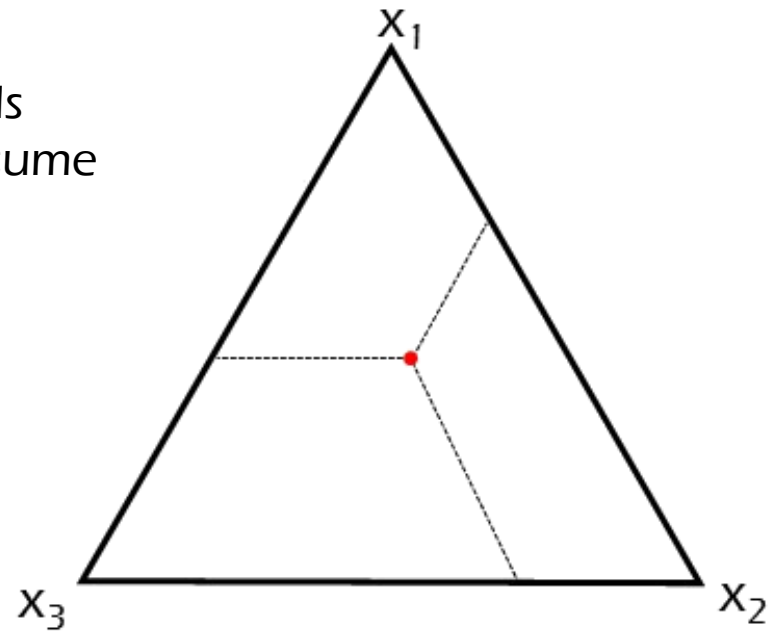
not to the amount of each system component, but to the proportion of components

(the components are complementary to each other)

there are restrictions on the levels (values) the components can assume

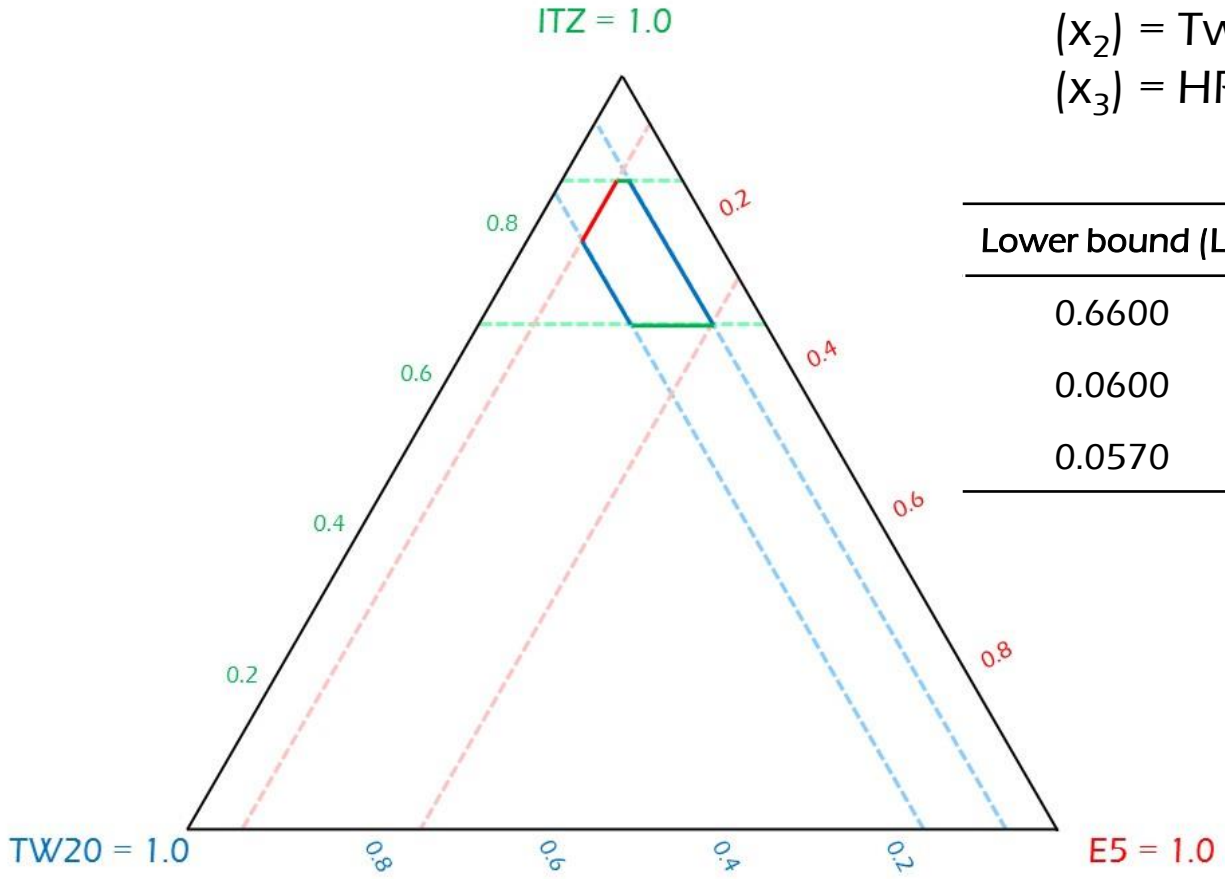
$$x_i \geq 0$$

$$\sum_{i=1}^{q} x_i = 1.0$$



Experimental design

Mixture Design



(x_1) = itraconazole (ITZ)
(x_2) = Tween 20 (TW20)
(x_3) = HPMC (E5)

Constraints:

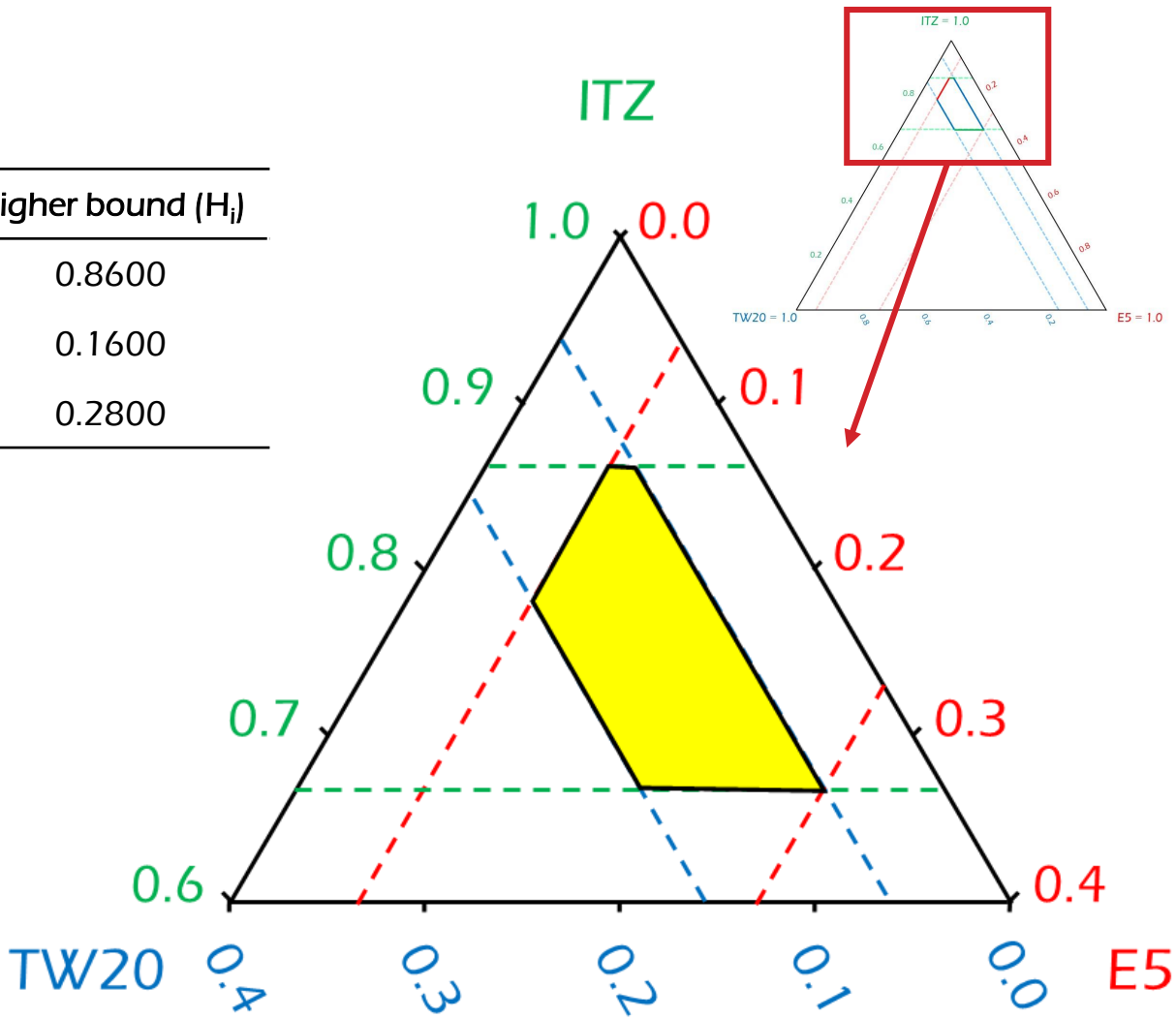
Lower bound (L_i)	Component	Higher bound (H_i)
0.6600	x_1 (ITZ)	0.8600
0.0600	x_2 (TW20)	0.1600
0.0570	x_3 (E5)	0.2800

Experimental design

Mixture Design

Constraints:

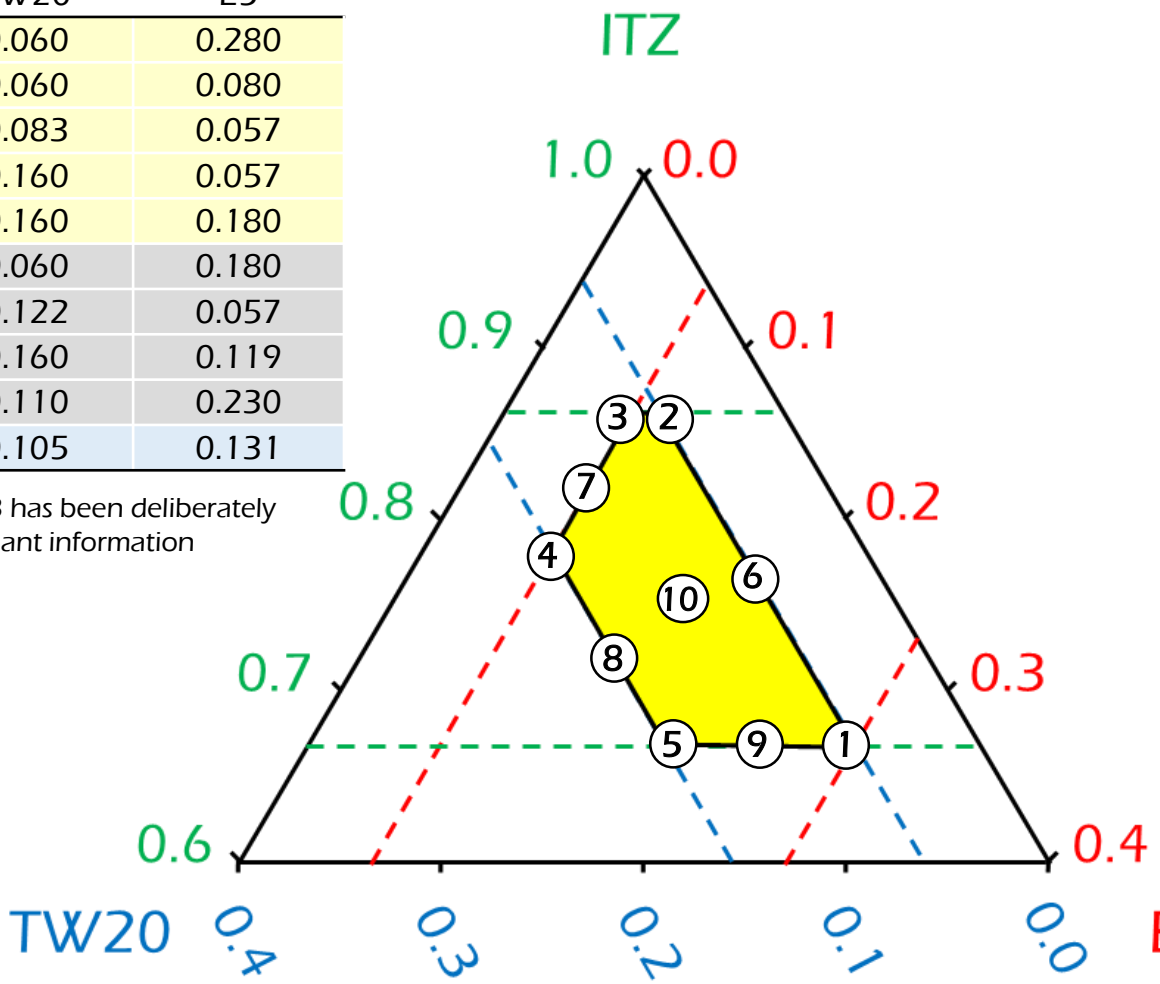
Lower bound (L_i)	Component	Higher bound (H_i)
0.6600	x_1 (ITZ)	0.8600
0.0600	x_2 (TW20)	0.1600
0.0570	x_3 (E5)	0.2800



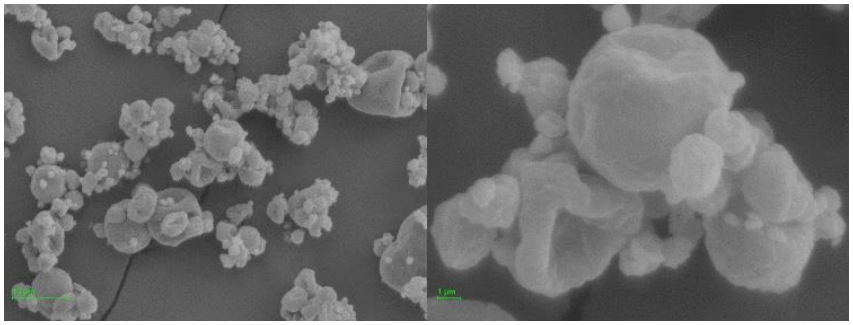
Setting of mixture design

Exp. point*	original coordinates		
	ITZ	TW20	E5
NS 1	0.660	0.060	0.280
NS 2	0.860	0.060	0.080
NS 3	0.860	0.083	0.057
NS 4	0.783	0.160	0.057
NS 5	0.660	0.160	0.180
NS 6	0.760	0.060	0.180
NS 7	0.822	0.122	0.057
NS 8	0.722	0.160	0.119
NS 9	0.660	0.110	0.230
NS 10	0.765	0.105	0.131

* the middle point on the edge 2-3 has been deliberately omitted because it gave no significant information



Characterization



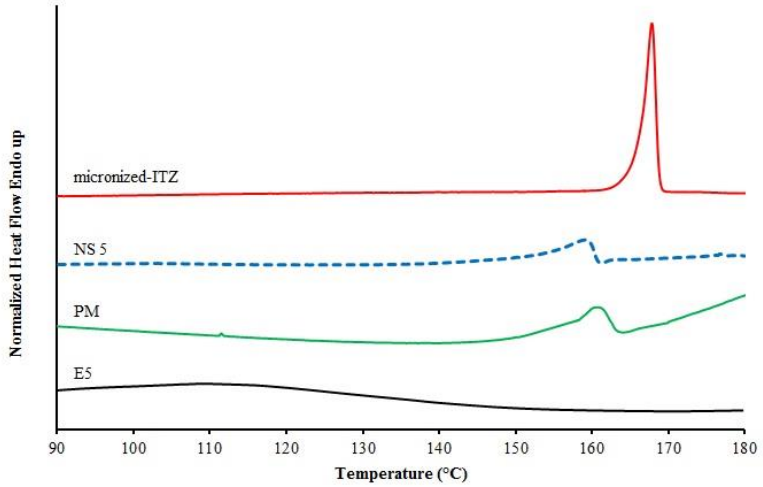
SEM

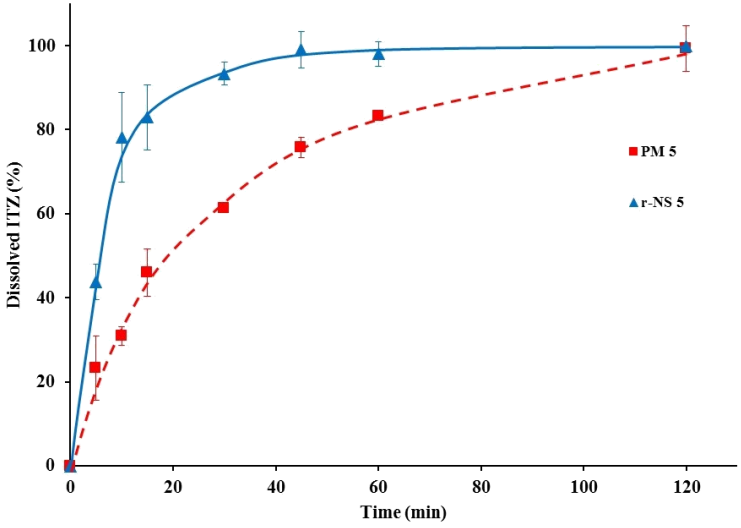
(dried nanosuspension)

DSC

Scan range = 90-180 °C

Scan rate = 5 °C/min





DISSOLUTION TEST

dissolution apparatus 2 USP

100 rpm, 37.0 ±0.5 °C, n=6

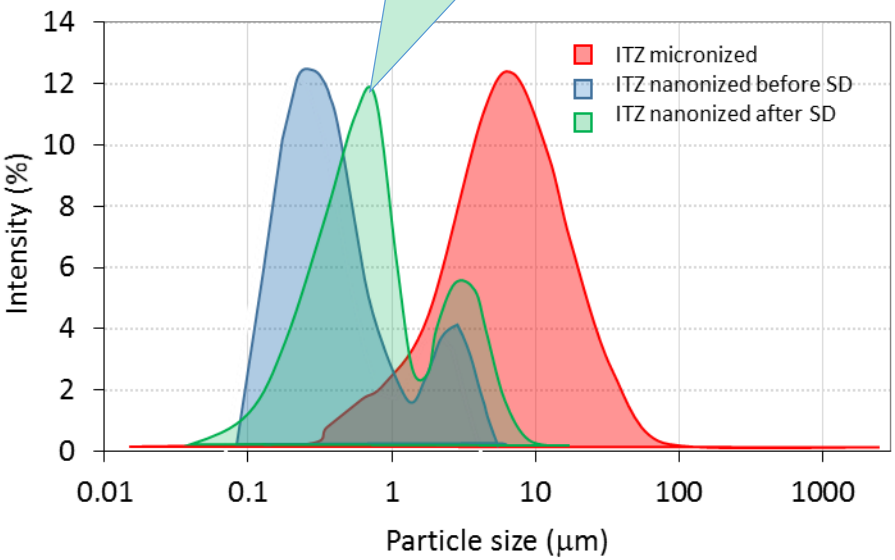
Introduction Methods Results

Characterization

PARTICLE SIZE – Z potential

Zetasizer 3000HS

on dried suspension after re-dispersion in *in use* conditions



system	Z_{pot} (mV)
ITZ micronized	**−32**
ITZ/TW20	**−30**
ITZ/TW20/E5	**−27**

Characterization

PARTICLE SIZE

Exp. point	N. of batches	Original coordinates			After HPH (NS system)		After SD (r-NS system)	
		ITZ	TW20	E5	Z_{ave} (nm)*	P.I.	Z_{ave} (nm)*	P.I.
1	3	0.6600	0.0600	0.2800	313.0	0.38	412.8	0.29
							439.0	0.30
							422.7	0.36
2	3	0.8600	0.0600	0.0800	338.6	0.41	731.1	1.00
							658.9	1.00
							721.3	1.00
3	3	0.8600	0.0830	0.0570	371.6	0.52	1105.3	1.00
							1248.1	1.00
							1091.5	1.00
4	3	0.7830	0.1600	0.0570	441.0	0.45	728.3	1.00
							675.2	0.96
							735.0	1.00
5	5	0.6600	0.1600	0.1800	439.5	0.37	447.8	0.46
							547.8	0.63
							509.2	0.72
							505.5	0.65
							492.0	0.69
6	3	0.7600	0.0600	0.1800	443.0	0.30	385.4	0.39
							409.2	0.56
							402.7	0.38
7	5	0.8215	0.1215	0.0570	455.9	0.40	1213.3	1.00
							1990.0	1.00
							1206.9	1.00
							1143.1	1.00
							1404.0	1.00
8	3	0.7215	0.1600	0.1185	379.9	0.36	445.4	0.37
							448.0	0.46
							427.6	0.43
9	3	0.6600	0.1100	0.2300	371.4	0.36	454.2	0.32
							433.8	0.34
							409.7	0.37
10	7	0.7646	0.1046	0.1308	368.1	0.33	432.4	0.44
							443.7	0.47
							437.5	0.48
							449.1	0.42
							528.5	0.90
							476.5	0.53
							432.5	0.52

*each value is the mean of two replicates

Model study

to study the relationship between the particles dimension and dried nanosuspension composition

Log transformation of the response (Z_{ave})

- to stabilize the residual variance
- to make the distribution of residuals closer to a normal distribution

Linear transformation of the original coordinates (x_1, x_2, x_3) in L-pseudocomponents (x_1', x_2', x_3')

- to obtain better graphics
- to make easier the fitting of data

Model study

Redefinition of coordinates of the subregion of interest

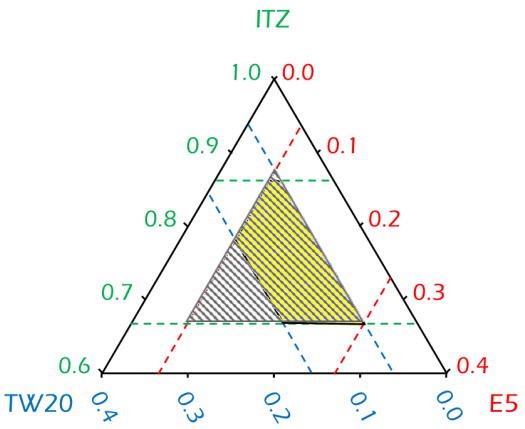
L-pseudo components

combination of the original components that takes into account the lower restrictions placed on each component

$$x_i' = \frac{x_i - L_i}{1 - \sum_{i=1}^{3} L_i}$$

Lower bound (L_i)	Component	Higher bound (H_i)
0.6600	x_1 (ITZ)	0.8600
0.0600	x_2 (TW20)	0.1600
0.0570	x_3 (E5)	0.2800

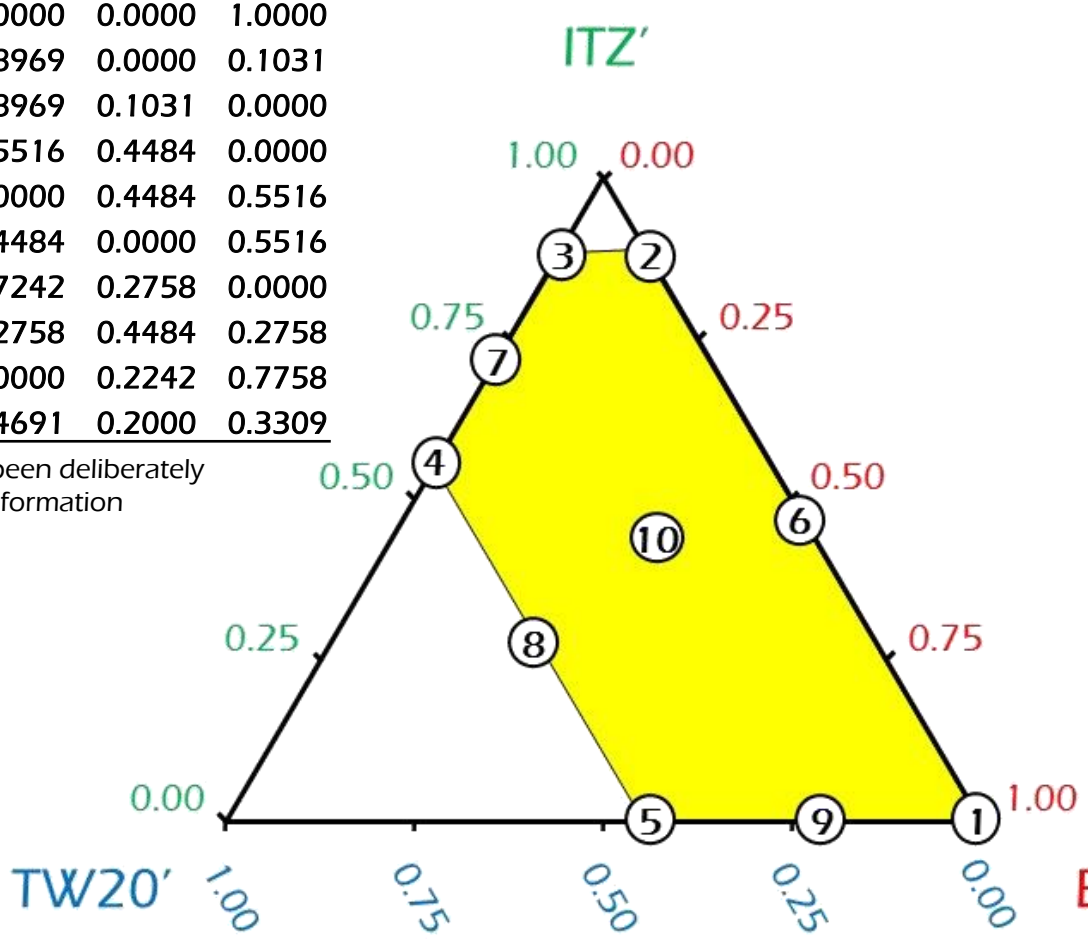
L-pseudo components



Setting of mixture design in the original components and in the L-pseudocomponents

Exp. point*	original component setting ITZ	TW20	E5	"L-pseudo"components ITZ	TW20	E5
NS 1	0.6600	0.0600	0.2800	0.0000	0.0000	1.0000
NS 2	0.8600	0.0600	0.0800	0.8969	0.0000	0.1031
NS 3	0.8600	0.0830	0.0570	0.8969	0.1031	0.0000
NS 4	0.7830	0.1600	0.0570	0.5516	0.4484	0.0000
NS 5	0.6600	0.1600	0.1800	0.0000	0.4484	0.5516
NS 6	0.7600	0.0600	0.1800	0.4484	0.0000	0.5516
NS 7	0.8215	0.1215	0.0570	0.7242	0.2758	0.0000
NS 8	0.7215	0.1600	0.1185	0.2758	0.4484	0.2758
NS 9	0.6600	0.1100	0.2300	0.0000	0.2242	0.7758
NS 10	0.7646	0.1046	0.1308	0.4691	0.2000	0.3309

* the middle point on the edge 2-3 has been deliberately omitted because it gave no significant information



Matrix of data for model calculation

r-NS exp. point	N. of batches	"L-pseudo" components			Z_{ave} (nm)*	Log Z_{ave}	P.I.
		ITZ	TW20	E5			
1	3	0.0000	0.0000	1.0000	412.8	2.616	0.29
					439.0	2.642	0.30
					422.7	2.626	0.36
2	3	0.8969	0.0000	0.1031	731.1	2.864	1.00
					658.9	2.819	1.00
					721.3	2.858	1.00
3	3	0.8969	0.1031	0.0000	1105.3	3.028	1.00
					1248.1	3.096	1.00
					1091.5	3.037	1.00
4	3	0.5516	0.4484	0.0000	728.3	2.862	1.00
					675.2	2.829	0.96
					735.0	2.865	1.00
5	5	0.0000	0.4484	0.5516	447.8	2.651	0.46
					547.8	2.738	0.63
					509.2	2.707	0.72
					505.5	2.704	0.65
					492.0	2.691	0.69
6	3	0.4484	0.000	0.5516	385.4	2.586	0.39
					409.2	2.612	0.56
					402.7	2.605	0.38
7	5	0.7242	0.2758	0.0000	1213.3	3.084	1.00
					1990.0	3.299	1.00
					1206.9	3.081	1.00
					1143.1	3.058	1.00
					1404.0	3.147	1.00
8	3	0.2758	0.4484	0.2758	445.4	2.649	0.37
					448.0	2.651	0.46
					427.6	2.631	0.43
9	3	0.0000	0.2242	0.7758	454.2	2.657	0.32
					433.8	2.637	0.34
					409.7	2.612	0.37
10	7	0.4691	0.2000	0.3309	432.4	2.636	0.44
					443.7	2.647	0.47
					437.5	2.641	0.48
					449.1	2.652	0.42
					528.5	2.723	0.90
					476.5	2.678	0.53
					432.5	2.636	0.52

*each value is the mean of two replicates

Fitting of data

The model:
special cubic Scheffé

$$LogZ_{ave} = b_1 ITZ' + b_2 TW20' + b_3 E5' + \\ + b_{12} ITZ' \cdot TW20' + b_{13} ITZ' \cdot E5' + b_{23} TW20' \cdot E5' + \\ + b_{123} ITZ' \cdot TW20' \cdot E5'$$

The analysis method:
cross-validated robust regression

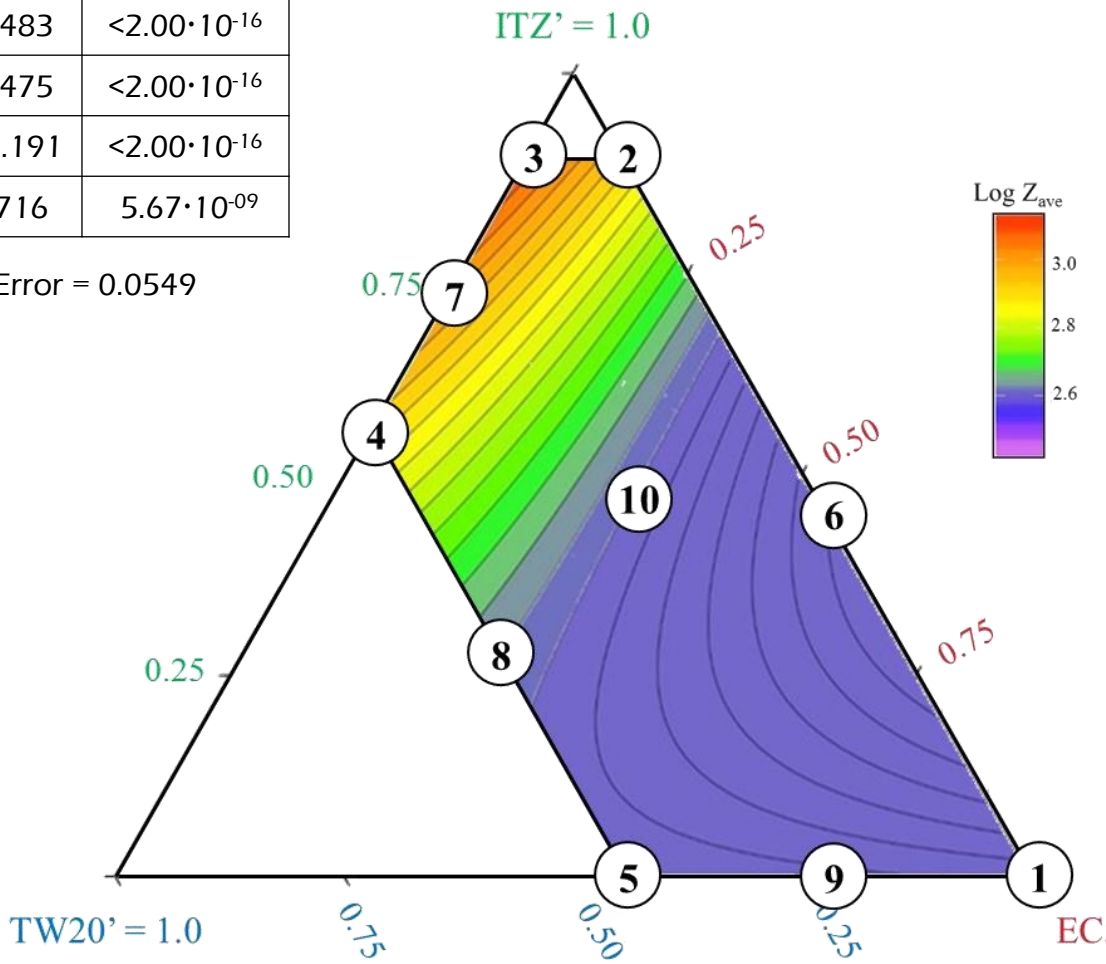
- not significant variables automatically deleted
- data weighed to reduce the influence of outliers

Coefficient estimates of reduced special cubic Scheffé model and related statistical parameters

Coefficient	Estimate	St. Error	t value	p
b_1	3.075	0.046	67.483	$<2.00 \cdot 10^{-16}$
b_2	2.687	0.045	59.475	$<2.00 \cdot 10^{-16}$
b_3	2.645	0.013	199.191	$<2.00 \cdot 10^{-16}$
b_{13}	-1.193	0.155	-7.716	$5.67 \cdot 10^{-09}$

$R^2 = 0.9996$; Adj $R^2 = 0.9995$; Res. St. Error = 0.0549

$p < 2.20 \cdot 10^{-13}$; $R^2_{CV} = 0.9021$

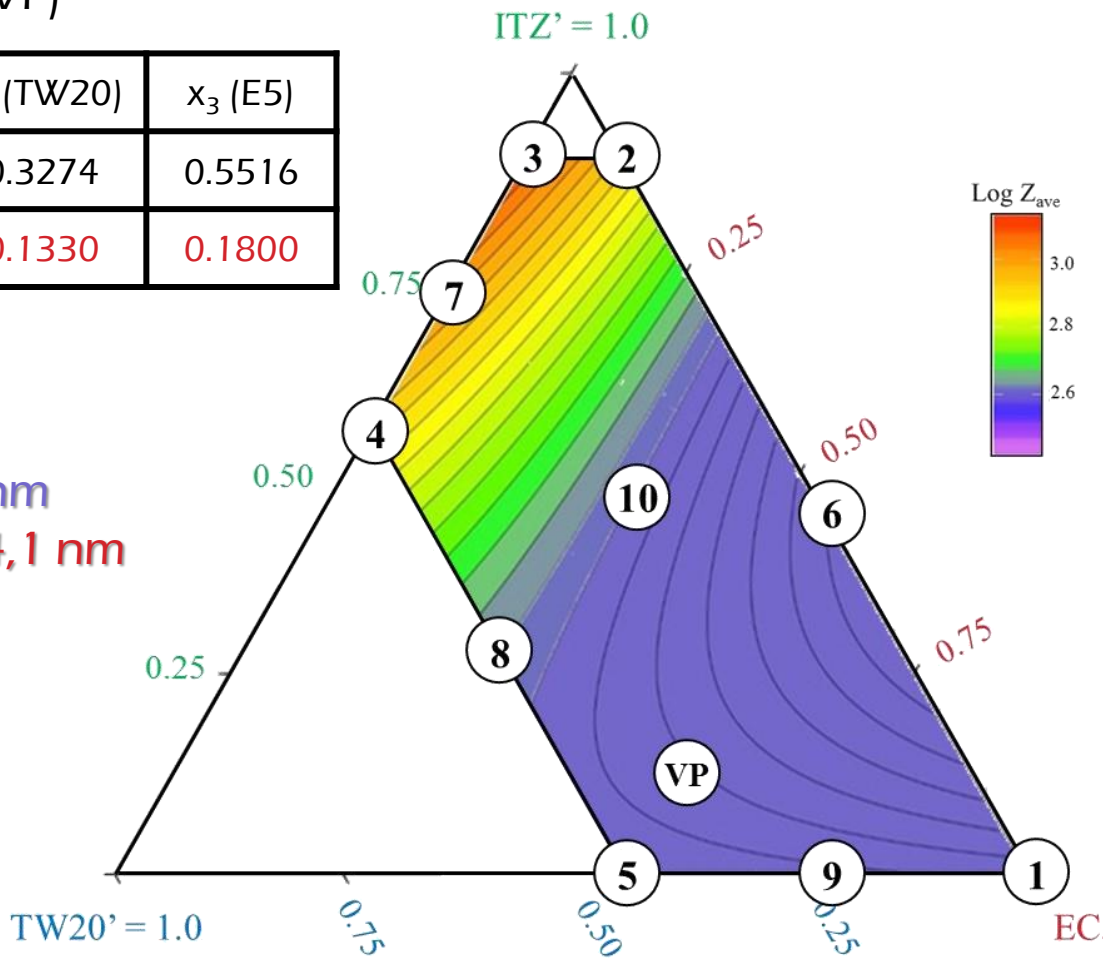


Prediction ability of the model

Validation Point (VP)

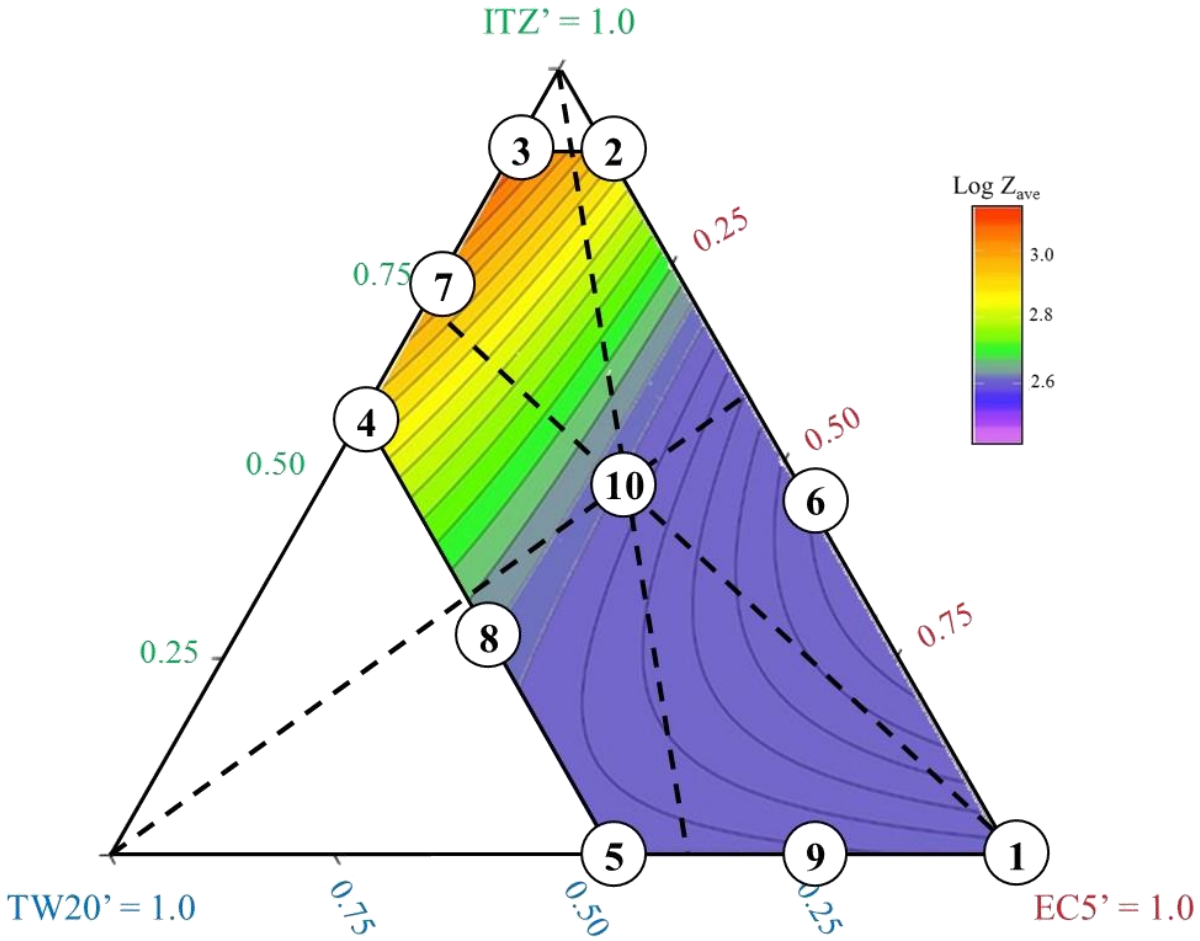
	x_1 (ITZ)	x_2 (TW20)	x_3 (E5)
L-pseudocomponents	0.1211	0.3274	0.5516
original setting	0.6870	0.1330	0.1800

predicted value = 429,2 nm
experimental value = 434,1 nm

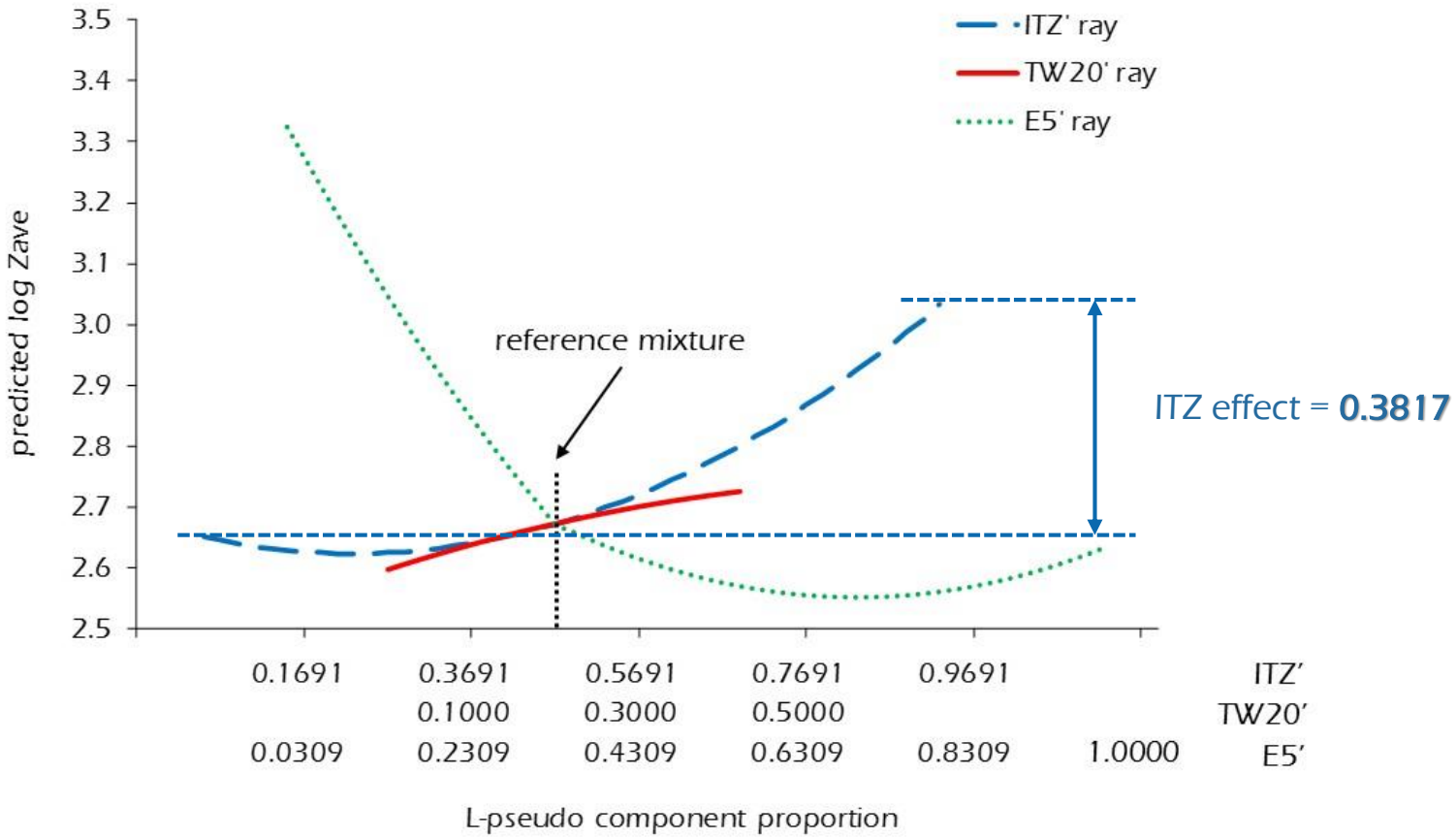


Effect of mixture components on the particle size

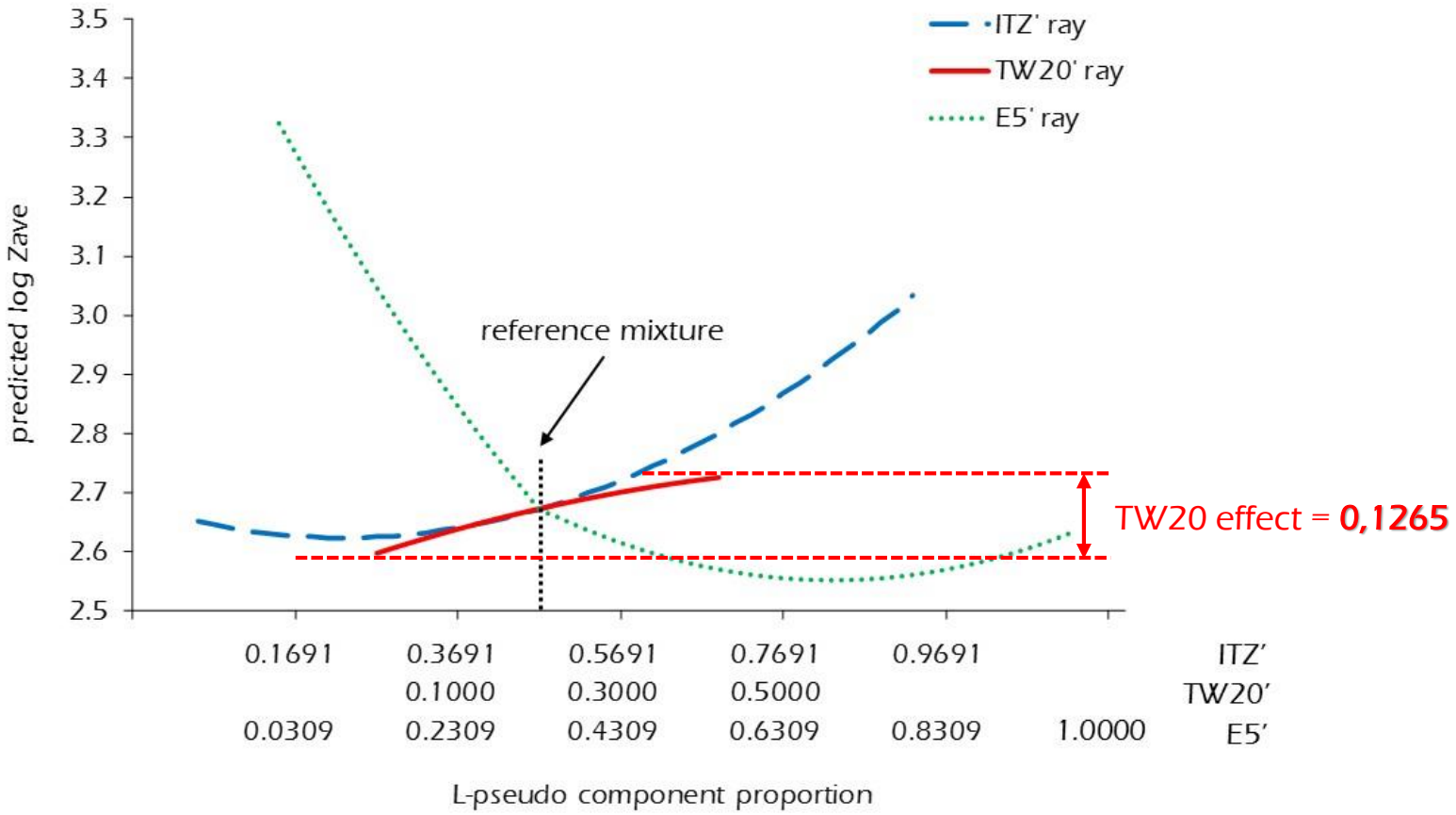
calculated along the **Piepel's directions** (along which the proportion of two components is constant)



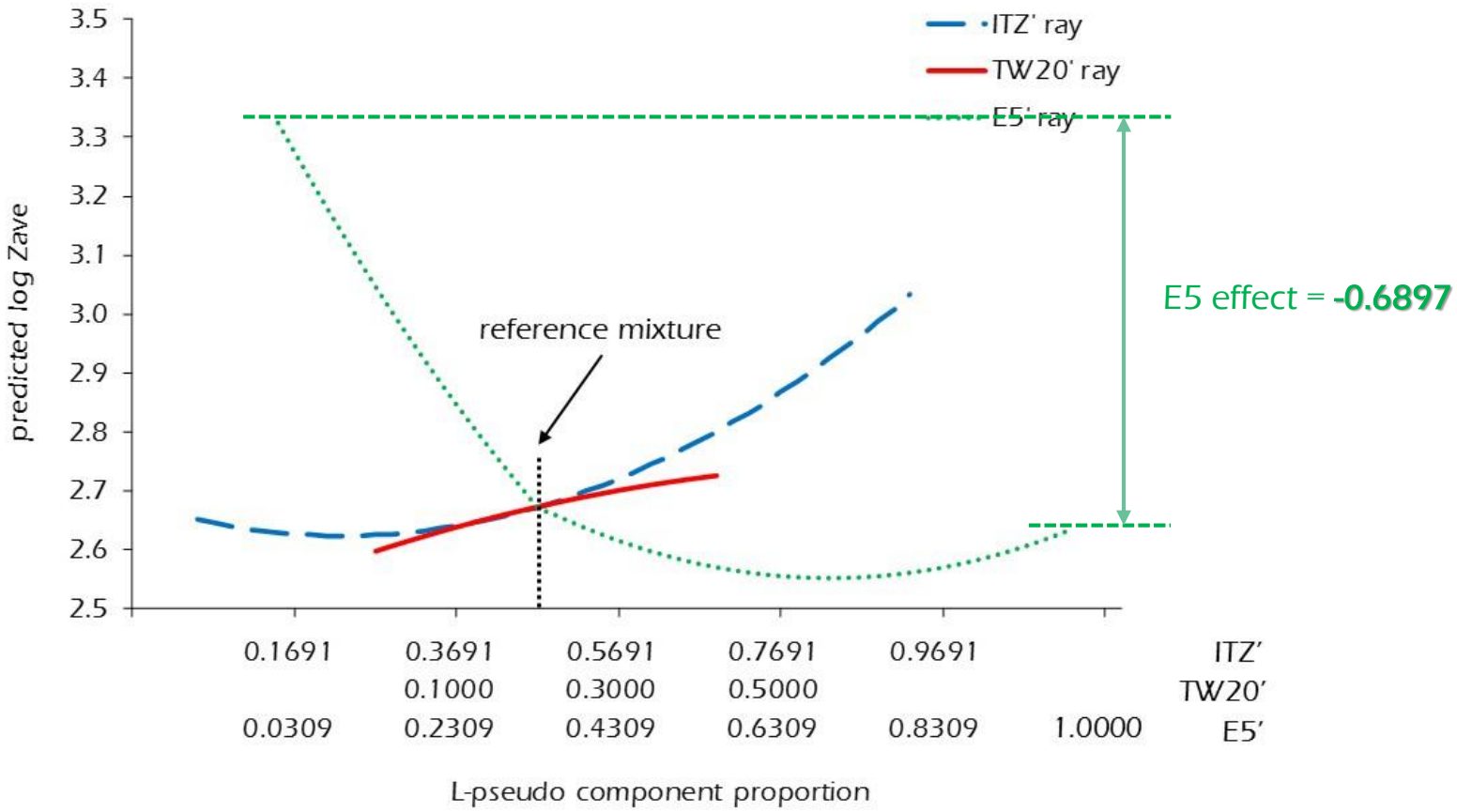
Effect of mixture components on the particle size



Effect of mixture components on the particle size



Effect of mixture components on the particle size



Conclusion

The obtained model

- describes with high accuracy the relationship between the size of nanocrystals and the proportion of components
- predicts the particle size of the nanosuspension with high reliability
- allows to evaluate the effect of the mixture components
- clarifies the role played by the suspension stabilizers

TW20: involved primarily in the comminution process

E5 (HPMC): responsible of re-dispersion and stability of ITZ nanosuspension

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