Selecting the right TiO_2/ZnO for performance and regulatory compliancy

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Introduction

As early as in 2006, European Commission (EC) recommended a critical wavelength of ≥ 370 nm and SPF/PFA ratio of ≤ 3 for claiming broad-spectrum protection. In 2011, FDA started to regulate UVA protection by requiring the same critical wavelength. Later in 2019, again in 2021, FDA added in their Proposed Orders an UVA-I/UV ratio of ≥ 0.7 as new criteria for claiming broad-spectrum protection for sunscreens.[1] As the regulation evolves, the sunscreen market has been gradually shifting to the use of inorganic UV filters such as TiO_2 and ZnO. In the FDA's proposed order, they are the only class I actives with GRASE status.

TiO_2 or ZnO are particulate materials and attenuate UV light through absorption and scattering, both of which depend on the particle size in the formulation. Size of their commercial grades varies widely from grade to grade, creating a challenge for predicting the balance in UVA/UVB protection and for complying with broad-spectrum requirement.

Materials and Testing:

TiO_2 or ZnO powders of various primary particle sizes (PPS) were surface treated and milled in dispersion to achieve the desired particle size (PS) of the aggregates. The particle size in dispersions was analyzed using a NICOMP C370 photo-correlation size analyzer. The mean size of intensity-weighted size distribution was used. The dispersions prepared were formulated in sunscreen compositions. SPF, CW and UVA-I/UV ratios were measured according to FDA's protocols. PFA was tested on 3 panelists according to the JCIA PPD method.

Results and discussions

1. Formulations using TiO_2 or ZnO

Table 1. Effect of Particle Size on UV Protection

	ZnO (W/O formula)						TiO_2 (O/W formula)		
Formula	Z-1	Z-2	Z-3	Z-4	Z-5	Z-6	T1A	T1	T2
PPS (nm)	263	~ 100	30	60	20	20	50	35	15
PS (nm) in Disp	320	263	228	163	166	130	162	154	125
Active (%)	15	16	14.97	14.97	14.97	13.80	10.29	10.29	10.29
SPF	12	12.6	14	20.4	17.4	25.4	25.6	28.4	50.0
CW (nm)	381	379	371	374	371	368	> 376	376	369.4
PFA	5.52	5.83	7.50	7.58	8.17	4.75	7.58	6.75	4.50
Label SPF/PFA	1.8	1.7	1.3	2.6	1.8	5.3	3.3	3.7	11.1

Table 2. Effect of Size on UVA-I/UV Ratio

	ZnO (15%) (W/O formula)			TiO_2 (10%) (Anhydrous)
Formula	Z-7B	F-A	F-B	AT-1
Dispersion	TN-1A	TN-2	TN-4	GT-1
PPS (nm)	20	35	60	35
PS (nm)	135	170	240	210
CW (nm)	369.8	375.5	385	378
UVA-I/UV ratio	0.78	0.85	0.96	0.77

Table 5. UVA-I/UV ratio for ZnO/Organic Combo

Formula (W/O)	F-G	ZO-2A	ZO-2C
SPF est.	**50**	**30**	**50**
ZnO Disp	TN-4 (PPSS 60, PS 240 nm)		
ZnO%	15	12.5	20
Octocrylene%	---	2	5
Homoslate%	10	--	--
Octisalate%	5	5	5
CW (nm)	375.7	377.5	376.5
UVA-I/UV ratio	0.55	0.76	0.77

Theoretical calculation by Stamatakis et al. shows that for submicron TiO_2 the UVB attenuation is predominately due to its absorption while the UVA attenuation is predominately due to its scattering, and the absorption of ZnO increases as particle size decreases across the entire UV region.[2] Our results in Table 1 show that ZnO can often provide broad-spectrum UV protection by both FDA and EU requirements but a moderate UVB protection. When the PS of ZnO was milled to be under 150 nm, it was efficient for SPF but the CW would decrease to under 370 nm. TiO_2 provided very high SPF but the transparent 15 nm could not provide sufficient UVA protection. In light of the proposed UVA-I/UV ratio of ≥0.7, ZnO always complies while TiO_2 needs to have a PPS of ~30 nm or higher, which may lead to some degree of whitening.

2. Formulating ZnO with organic sunscreen actives

Results in Table 3 shows that increasing size of nano ZnO has little impact on the CW of ZnO/Organic hybrid system. It is surprising to see that CW did not increase at all even when homosalate was reduced from 12% to 0%. In our effort to reach a CW of 370 nm, ZnO dispersion of relatively large PPS of 60 nm, GC-5, was used at different levels. In combination with octinoxate and octocrylene, 12.5% of ZnO had to be used (Table 4). Again, change in octocrylene level had little effect on the CW.

Table 3. CW of ZnO/Organic Active-Set 1

ZnO 7.5%; Octinoxate 7.5%, Octocrylene 2%			Homosalate %			
			12	6	3	0
Dispersion	**PPS (nm)**	**PS (nm)**	**CW (nm)**			
GC-3	20	206	367	361	364	362
GC-4	40	238	368	370	-	-
GC-5	60	241	368	367	-	-

Formula	Octinoxate	Octocrylene	ZnO (GC-5)	CW (nm)
ZO-2A	7.50%	2%	7.50%	367.5
ZO-2C	7.5%	2%	10%	369.6
ZO-2D		0%	10%	370.7
ZO-2E	7.5%	2%	12.50%	370.3
ZO-2F		1%	12.50%	371.4

Anticipating the challenge to get an UVA-I/UV ratio of 0.7, 60 nm ZnO was selected based the CW study (Table 5). When ZnO was used at 2x the amount of organic sunscreen actives, the ratio went beyond 0.7. It is strange to see that formula F-G has a CW of 375.7 nm but the ratio is only 0.55, showing a different behavior from formulas ZO-2A and ZO-2C. More testing is needed to understand this discrepancy.

3. Formulating ZnO with TiO_2

Ultrafine (10-20 nm) TiO_2 provide weak UV protection. But when used with ZnO at 2.5 times its level, the CW easily reached 370 nm (Table 6). However, to reach UVA-I/UV ratio of 0.7, ZnO needed to be more than 3 times the TiO_2 amount as data in Table 7 indicates. Formula TZ-6 has a very high CW of 377.1 nm, a UVA-I/UV ratio of 0.7 and in-vivo SPF of 31.

Table 6. CW for 5% TiO_2/12.5% ZnO Combo

Formula	ZnO Disp	PPS (nm)	PS (nm)	SPF	PA	CW (nm)
TZ-1	TN-2	20	165	31	11	368
TZ-2	TN-3	20	221	--	--	372
TZ-3	TN-4	60	238	--	--	373

Table 7. UVA-I/UV Ratio for TiO_2/ZnO Combo

Formula (W/O)	F-G	TZ-5	TZ-6
TiO_2 (PS 125 nm)	5%	5%	4%
ZnO (TN-4)	12.50%	15%	15%
CW (nm)	375.7	375.6	377.1
UVA-I/UV ratio	0.65	0.68	0.7

Conclusions:

Ultrafine TiO_2 provide strong UVB protection. It can also provide broad-spectrum protection by FDA proposed requirement when the primary size is 30 nm or larger, which may leave a white case on the skin. ZnO in general provides broad-spectrum protection but SPF is often moderate. It can be made to provide high SPF but at the loss of UVA protection. For broad-spectrum yet high SPF protection, TiO_2/ZnO combination can be easily formulated. For ZnO/Organic hybrid sunscreen system, the CW and the UVA-I/UV ratio cannot be easily predicted because the synergy in UVA and UVB is complex. Nonetheless, our study clearly indicates that in any hybrid system high level of ZnO, 3 times the amount of other UVB sunscreen actives, is often needed to comply with the FDA proposed broad-spectrum requirement.

References:

1. Amending OTC Monograph M020: *Sunscreen drug products for OTC human use*, FDA, September 24, 2021
2. P. Stamatakis and B. R. Palmer, *J. Coating Tech.* , Vol. 62, No. 789, p95, October, 1990