

Determining the Contribution of Individual Active to SPF - a Proposed Methodology

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The Final Monograph of the FDA Regulation for Sunscreen Drug Products for Over-The-Counter Human Useⁱ includes a requirement that each active in a sunscreen formulation shall contribute at least a value of 2 to the SPF of the final formulation. The document does not proscribe how this contribution by an individual ingredient to the SPF is to be determined. Use of the FDA Monograph SPF Test method is expensive, as the presumption is that SPF of each active in the chosen excipient base would need to be determined against a full panel of test subjects. Additionally, it is not always possible to prepare combinations that present suitably for application to human test skin, when one of the major sunscreen agents is excluded from the formula.

SPF measures UVB protection. UVA filters rarely exhibit much contribution to the SPF except by allowing UVB filters to more fully cover the UVB range. Maximum SPF values are obtained by fully absorbing UVB radiation from 290 to 320 nm.

Typically SPF yield values for individual sunscreen actives fall within the range of 0.5 to 1.5%. However, it is well known that combinations of sunscreens can work synergistically to extend the SPF well above the expected contribution of each individual active.^{ii, iii} For example, the SPF 15 control formulation included in the COLIPA test method, and utilised in this experiment, yields a SPF of 15 for a total content of around 6.5% of actives with theoretical yield values unlikely to total more than about 9. Similarly, the F 1 Homosalate Reference Sunscreen of the FDA method has a content of 8% active, with an SPF of only 4. Thus, it cannot be assumed that the addition of 1% of an active will add only about one SPF units to the total SPF of the formulated product.

It is the experience of the authors and othersⁱⁱ that sunscreens are not formulated in a systematic fashion, beginning with one active, which is then optimised before addition of further actives. More typically, sunscreens are formulated with an initial combination of actives which are selected from experience, with consideration of regulatory limits to maximum content, for performance over specific areas of the spectra and for known synergistic contribution. Thus, a methodology which determines SPF contribution of each chosen active would appear not to be appropriate or economical for product development.

We propose an *in-vitro* methodology for determining this contribution, based on determination by subtraction. That is to say, by removing only one active from the formulation and thus determining its contribution to the SPF by difference. The proposed methodology can thus be applied retrospectively, once the total performance of final formulation has been confirmed.

Methodology

The instrumental *in-vitro* methodology is based on the principle described by Diffey and Robson^{iv}. A Shimadzu UV-2450 Spectrophotometer fitted with an integrating sphere device, was utilised. The absorbance was measured in the range 400nm and 290nm. The *in-vitro* SPF was determined by utilising the values provided in the CIE Journal 6, 17-22 (1987)^v "A reference action Spectrum for ultraviolet induced erythema in human skin", adopted by the Commission on Illumination (CIE). Values of PF contribution were calculated at 5 nm intervals to arrive at an estimation of *in-vitro* SPF.

Additionally, the estimated *in-vitro* SPF was factorised by applying the actual SPF as determined *in-vivo*, to the area under the absorption curve for the complete formulation sample, to extrapolate the variance for each active deficient sample. Two standard sunscreens were utilised for the study. The first was the SPF 15 Reference Sunscreen utilised in the COLIPA^{vi} and Australian^{vii} SPF test methods. This preparation contains 3 actives - 3% Ethylhexyl Methoxycinnamate (INCI designation) (Octinoxate- USAN name) (OMC is the abbreviation used in this paper) 0.5% Butyl Methoxydibenzoylmethane (INCI designation) (Avobenzone- USAN name) (BMBM for this paper) and 2.78% Phenylbenzimidazole sulfonic acid (INCI designation), (Ensulizole - USAN name) (PBSA for this paper). The second was the SPF 4 Reference Sunscreen as described in the FDA Monograph. This formulation contains 8% of Homosalate as the only active.

A series of samples were prepared, each omitting one of the actives, together with a sample of the complete formulation. Additionally, a placebo containing no actives was prepared to match each formulation. Purified Water replaced the actives in each case. 2 methods of sample preparation were utilised.

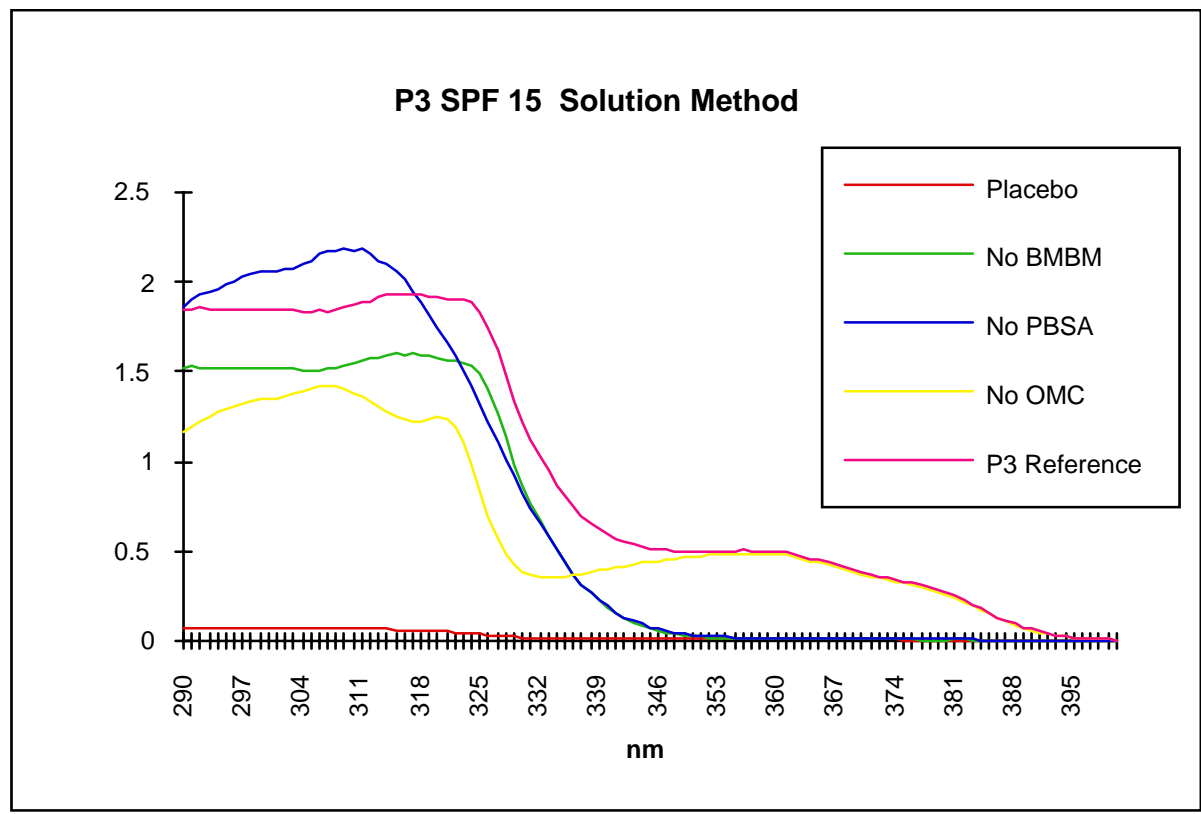
1. Solvent Solution Method.

This method is documented in the AS/NZS Standard ^{vi} for the determination of broad spectrum and is suitable for use with products which form a clear solution in a mixed solvent consisting of spectrophotometric grades of Dichloromethane, Cyclohexane and Isopropanol. The sample was diluted to a concentration of 0.8mg/mL by dissolving 40mg and making to volume with the mixed solvent. A matched cell containing solvent only was placed in the reference beam.

2. Dry Film Method on PMMA Substrate

The second preparation, base on the SPF Reference Sunscreen was also tested by a dry film method. Abraded Polymethylmethacrylate (PMMA) slides were prepared and a thin film of 2 mg/sq cm was applied and the sample set in the spectrophotometer. A blank slide coated with Glycerin was placed in the reference beam of the spectrophotometer. UV Chromatograms for each formulation and method are included below.

P3 SPF 15 Reference Sunscreen – Method 1 (Solution)



P3 SPF 15 Reference Sunscreen – Method 2 (PMMA plate)

These *in-vitro* results are tabulated below, together with the *in-vivo* SPF as extrapolated from the adjusted SPF value for each standard formulation as determined (SPF 15.2 or 4.2). The effect of the placebo was also confirmed *in- vivo*.

Results

SPF 15 Reference Sunscreen

	In Solution	Corrected	On PMMA Plates	Corrected	SPF in Vivo
SPF 15 (Complete formula)	21.7	15.0	16.5	15.0	15.0
Placebo	1.1	0.8	0.9	0.8	1.6
No BMBM	9.9	6.9	5.8	5.3	
No PBSA	12.1	8.5	8.0	7.3	
No OMC	11.2	7.8	3.6	3.3	

F1 SPF 4 Reference Sunscreen

SPF 4 (Homosalate)	6.1	4.2	7.8	4.2	4.2
Placebo	1.1	0.8	1.1	0.6	1.1

Calculation of SPF Contribution

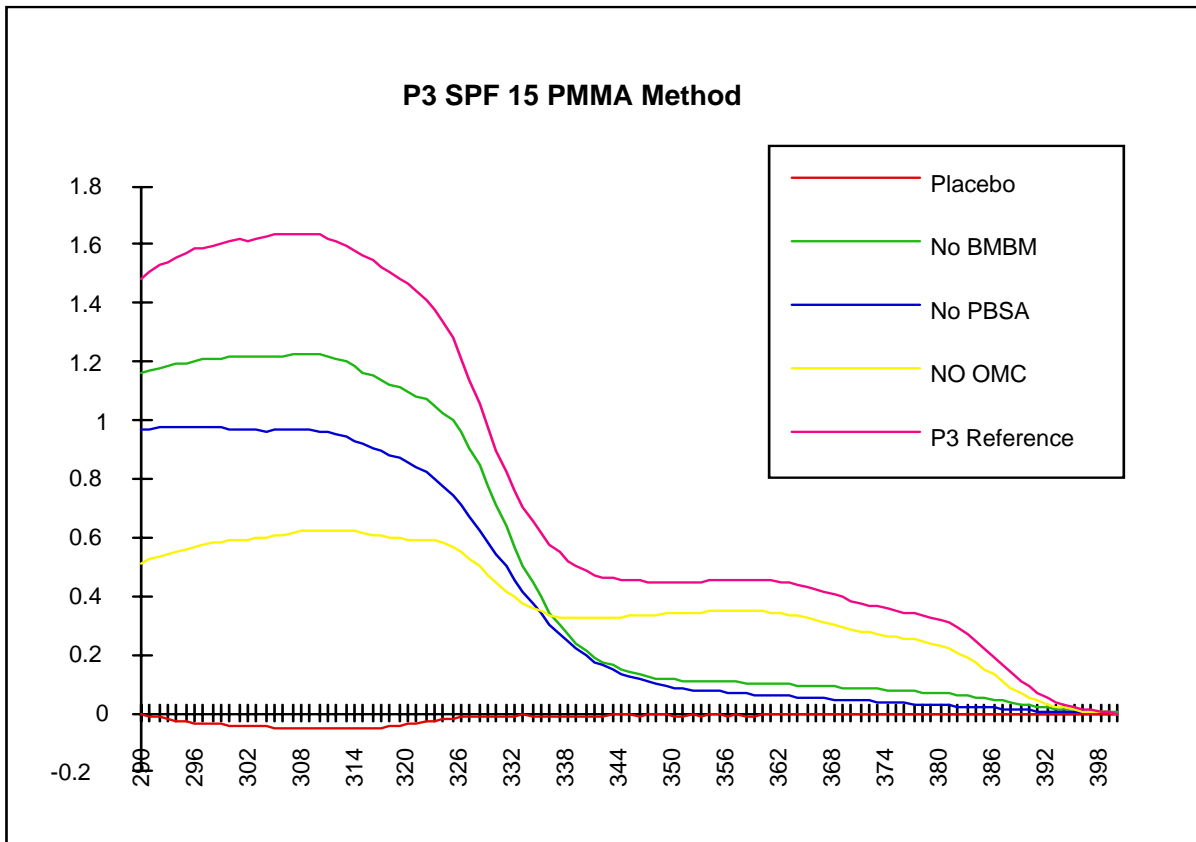
SPF 15 Sunscreen

	In Solution	On PMMA Plates
0.5% BMBM	8.1	9.7
2.78% PBSA	6.5	7.7
3% OMC	11.4	11.7

Discussion

Presentation of samples

The spectra obtained from the PMMA plates appear to be consistent with what would be the standard spectra for the individual actives. The spectra for the Solution method appear to be altered, possibly due to bathochromic shift and hypochromic effect, due to the solvents present. This method would appear to be inappropriate, even though the final calculation of SPF contribution is



similar to the PMMA series.

As the SPF value for the samples with one active removed, is always related to the actual SPF value determined in-vivo, solution concentration or sample film thickness is more dictated by instrumental needs than by the need to reproduce the (2mg/sq cm) application rate used in in-vivo test methods^{i,vi,vii}. A thinner film thickness may be more appropriate to higher SPF products, or to those incorporating inorganics, so as not to exceed the sensitivity limits of the measurement instrument. As the in-vitro estimation of SPF is corrected for the in-vitro value as determined for the complete formulation, sample quantity becomes less relevant.

Measurement of a placebo should not be necessary for most formulations, as this is not included in *in-vivo* measurement and the impact is unlikely to influence the determination of SPF contribution.

Suitability of Instrument

Collaborative inter-laboratory studies conducted by the Task Force of the DKG (German Society for Scientific and Applied Cosmetics)^{viii} have shown that a number of similar instruments are suited for this methodology. For measurement of films, an integrating sphere device must be incorporated in the instrumental configuration.

Impact of Formulation Types

This needs further investigation with a larger study, but the most likely limitations will relate to stability of the varied formulation, due to remove of an active.

Conclusion

The study indicates that the approach of subtraction of each single active and use of standard in-vitro methodology may be suitable for estimation of contribution of such individual active to the total SPF of the product. We propose the utility of the method for providing evidence in support of the FDA requirement for SPF contribution of each individual active.

References

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