

perature during drying, thereby reducing color bleeding and case hardening effects, and facilitating the handling of heat sensitive materials.

4. Decreased handling costs resulting from simplified loading and unloading operations.

5. Simplification of tablet manufacturing procedures by the possible elimination of grinding steps. Opportunities may also exist for blending lubricants and other materials into dry granulations directly in the fluidized bed.

Fluidized drying beds of small capacity appear to have further significant usefulness in research operations for routine testing of new tablet formulas on a rapid basis.

Because of the extensive application in other industries of the fluidized bed drying technique, it is reasonable to assume that the conclusions of this report are not limited to the prototype granulations actually tested. The Glatt dryer used in this study represents a significant improvement over conventional tray dryers. The present data suggest, however, that the drying performance of this unit is not as high as that which can be expected from fluidized bed dryers.

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Psychophysical Concept of Color

By ALLAN M. RAFF

Color has been defined as a psychophysical concept by the Committee on Colorimetry of the Optical Society of America. The concept of the Commission Internationale de l'Eclairage (C.I.E.) standard human observer is discussed, which illustrates the color sensitivity curves on which the C.I.E. color triangle is based. Examples are given which show the variance in results that occur in color stability studies when a "standard observer" is used as opposed to an evaluation made solely on the basis of spectrophotometric data. Several standard techniques for evaluating small color differences are reviewed.

WITHIN the last several years the stability studies of pharmaceutical products have become increasingly more sophisticated. The use of kinetics, cyclization of temperatures, and more advanced forms of instrumentation are just a few of the things that have brought the study of the chemical stability of pharmaceutical products to a very high level.

This same high level has yet to be reached in the matter of color stability studies. This deficiency may be due to two causes. The first cause has been a lack of the need for such studies

until recent times. Until the FDA decertified some dyes and indicated a prospect for the decertification of several more, the pharmaceutical formulator had a relatively easy task. He had only to choose the most stable dye from a long list of dyes and color his product. Today he has the task of determining which of several very photosensitive dyes is the most stable. He must also make matches of colors heretofore achieved with one dye (perhaps now decertified), now with different colorants. The second cause of the deficiency noted is due in a very large part to a complete misunderstanding of the concept of color as it should be used in pharmaceutical stability studies.

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METHODOLOGY

The increased need of color stability studies has brought about a corresponding increase in the application of scientific methodology to this field. There have been several studies (1-6) reported which utilize such techniques as kinetics, advanced instrumentation, and reproducible methods of fading pharmaceutical dosage samples. Investigations such as these have alleviated one of the causes of unsophisticated color stability studies. However, even these investigations may be inconclusive because none of them have treated color as a psychophysical concept.

If we stop short of this concept, *i.e.*, if we confine all of our color studies to an instrumental level, then we have not, in reality, made a study of color stability.

Concepts of Color.—As defined by the Optical Society of America (7), "Color consists of the characteristics of light other than spatial and temporal inhomogeneities; light being that aspect of radiant energy of which a human observer is aware through the visual sensations which arise from the stimulation of the retina of the eye." This concept is reiterated in one form or another in other references in the field of color measurement (8-13).

Nickerson (14) states that: "It is true that a spectral distribution curve may serve to define unambiguously the *stimulus* for the color of a light source, but the spectral-reflectance or spectral-transmittance curve of an object is not sufficient to define even the stimulus for its color. Its spectral properties must be combined with those of the light source under which it is to be viewed before even the stimulus for the object's color is defined. To define its *color* the concept of an observer must also be introduced."

The *Ciba Review* (15) expresses this concept: "Measurement of the spectral reflection curves of typical colored surfaces shows, as we should expect, that a red surface has a high reflection at the red end of the spectrum, but a low reflection in the green and blue. A green surface has its maximum reflection in the green, and a blue surface in the blue. Consideration of the reflection curve for a yellow surface, however, shows that *this correlation is of limited application*, since a yellow surface is nearly as efficient in reflecting the green and red wavelengths as it is the narrow band of yellow wavelengths around 0.58 μ . *Clearly, an adequate interpretation must take account of the combined effect in the eye of all the wavelengths reflected by the surface.*"¹

This consideration of color as a psychophysical concept is of more than academic interest in pharmaceutical formulating and in the resultant color stability studies of these products. Colorants are added to various pharmaceutical dosage forms, unlike the active ingredients, primarily for their esthetic effect and as a means of identification. When one assays for the active constituent in a product and it is found to be only 50% of theory then this may be, with a fair degree of certainty, interpreted to mean that there will only be 50% of the desired therapeutic response. However, if one determines by a spectrophotometric assay that a green colorant has decreased in concentration by a

numerical value of 10% and a yellow colorant has also decreased by an equal amount, one cannot say without performing certain mathematical transformations that these two colorants will *appear* to a *human observer* to have faded equal amounts. Since the relationship between the visual appearance of colors is what one is really attempting to establish when color stability studies are done, it is of the utmost importance that the concept of the human observer be brought into consideration.

EXPERIMENTAL

In order to illustrate the errors that may occur when we attempt to evaluate color solely on the basis of spectrophotometric data, the following study is presented.² Test panels containing pigments were exposed to sunlight, and after several months exposed and unexposed panels were measured on a G.E. recording spectrophotometer equipped with a Librascope automatic integrator. Color differences were calculated using the Godlove formula (16) and the results expressed in N.B.S. units (10, 17, 18, appendix of this article³).

Figures 1-5 illustrate the reflectance measurements on control and exposed panels of violet, green, yellow, orange, and red pigment colorants, respectively. Figures 6 and 7 are the reflectance curves of Figs. 2 and 3, respectively, mathematically transformed into "absorbance" units.

It may be seen from these figures and the compilation in Table I that no correlation can be made,

TABLE I.—REFLECTANCE AND "ABSORBANCE" DIFFERENCES vs. COLOR CHANGE

Color	Color Change N.B.S. Units	Per Cent Difference in Reflectance ^a at Max. at Min.	Difference in Absorbance ^a at Max.
Violet	5	1 1	
Green	5	0 5	0.068 ^b
Yellow	6	6 1	-0.028 ^b
Orange	4	5 1	
Red	5	1 1	

^a Value of control minus that of exposed. ^b Absorbance units.

by a visual inspection of the curves, between a change in reflectance (or so-called absorbance) and the change in color that one will perceive.

All five of these colorants have changed to different degrees, but their appearances are essentially the same in terms of visual perception.

The pigments chosen yielded relatively simple curves. Other colorants and mixtures of colorants that display more than one maximum or exhibit metamerism would be even more illustrative of this lack of correlation.

In view of this demonstrated lack of correlation between reflectance curves and the color perceived by a human observer, the author believes that it is the responsibility of the investigator reporting on

¹ These test panels and the evaluation of their color differences in N.B.S. units were a part of a study made by Vincent C. Vesce, while technical director of Harmon Colors, National Aniline Division, Allied Chemical Corp. (19). I wish to thank Mr. Max Saltzman of National Aniline Division of Allied Chemical Corp. for allowing the use of these data and his very generous giving of his time and assistance to the author.

² A brief review of the techniques useful to those engaged in color studies is presented in an appendix to this article and is available from the author.

¹ Italics those of the author.

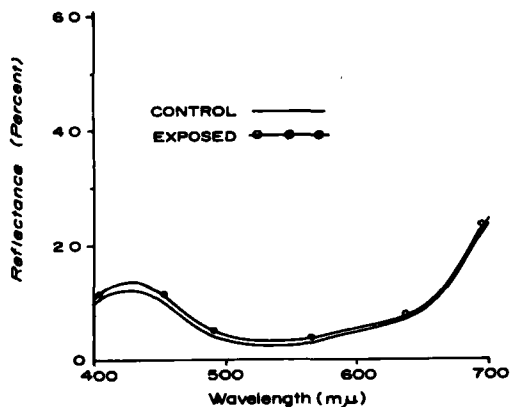


Fig. 1—Reflectance measurement of a violet pigment; Color Index No. 60016; color change is 5 N.B.S. units.

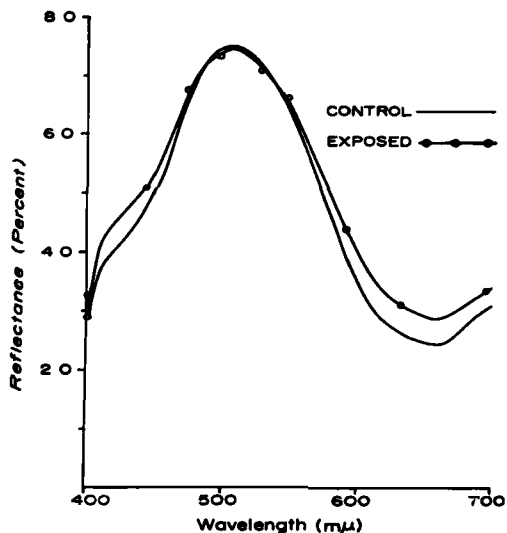


Fig. 2—Reflectance measurement of a green pigment; Color Index No. 74120; color change is 5 N.B.S. units.

color studies to prove that where it is utilized, a single wavelength determination is valid in each and every case studied. This is not to say that a single wavelength cannot be utilized to follow the course of a colorant change, but it must be substantiated by sufficient data to prove its validity. This method of using a single wavelength determination has been used, for example, by McLaren (20). He states, however, "This method of determining the degree of fading is only very rough; greater accuracy could have been achieved if the Kubelka-Munk equation or the best of the American colour difference formulas had been used. Such methods would have taken very much longer, however, and did not appear essential in view of the elementary nature of the investigation."

A failure to transform spectrophotometric data into some system which takes into account the sensitivity of the eye in conjunction with a specific light source will also, in some instances, invalidate

those studies that attempt to rank different colorants with regards to their resistance to fading.

Other Experiments.—Urbanyi, *et al.* (3), measure the reflectance of opaque objects in terms of absorbance, yet absorbance is, by definition, the negative log of transmittance.

In dealing with transmission data the values of the various concentrations follow Beer's law. Absorbance ($-\log T$) is directly proportional to concentration. For reflectance work, two ordinate scales are in use. The linear scale is the most common, but has the same limitations as the linear scale in transmittance work. Reflectance data at various concentrations follow an entirely different scheme which may be termed the K/S rule. Kubelka and Munk

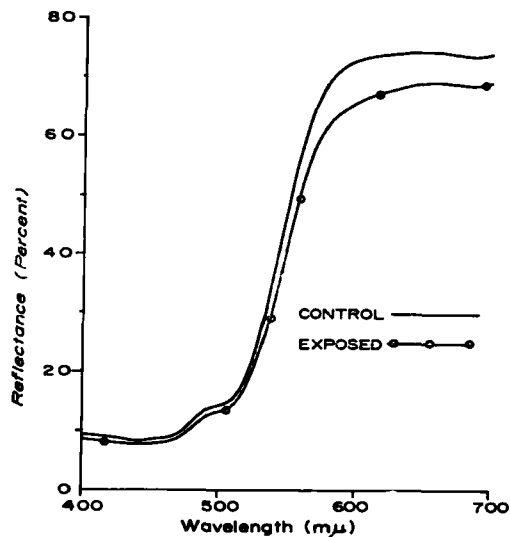


Fig. 3—Reflectance measurement of a yellow pigment; Color Index No. 70600; color change is 6 N.B.S. units.

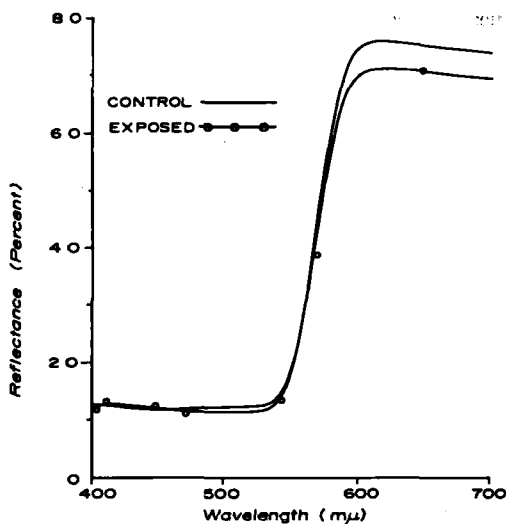


Fig. 4—Reflectance measurement of an orange pigment; Color Index No. 11725; color change is 4 N.B.S. units.

(10, 21, 22) defined monochromatic reflectivity as

$$K/S = \frac{(1 - R_{\infty})^2}{2R_{\infty}}$$

where:

$$R_{\infty} = 1 + (K/S) - [(K/S)^2 + 2(K/S)]^{1/2}$$

K = absorption coefficient or fraction of the incident energy lost by absorption per unit thickness of material, while S = scattering coefficient or fraction of the incident energy lost due to scattering per unit thickness of material.

This theory has been extended by others, showing that within limits, the dye and a matrix material absorb and scatter light independently of one another and that the ratio K/S for the dye (as distinct from K/S for the matrix material) bears a proportionality to the amount of dye present.

Urbanyi further utilizes a tristimulus technique measuring the color of opaque objects at only three wavelengths. The tristimulus values are normally computed by integrating the product of the ordinates

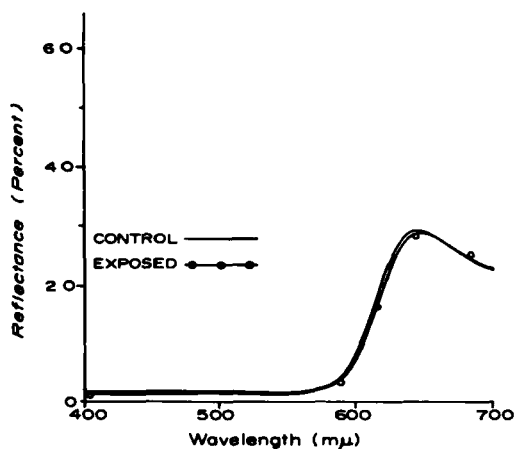


Fig. 5.—Reflectance measurement of a red pigment; Color Index No. 15865; color change is 5 N.B.S. units.

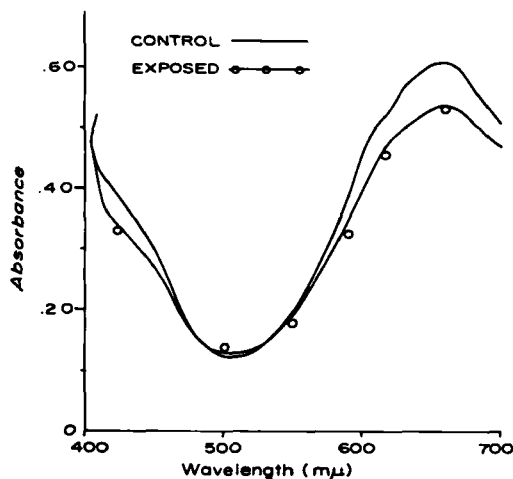


Fig. 6.—Reflectance data of Fig. 2 mathematically transformed into "absorbance" units and replotted.

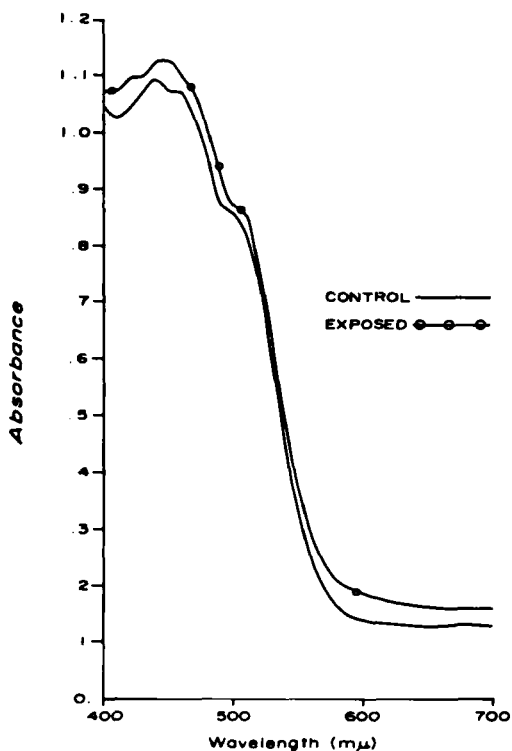


Fig. 7.—Reflectance data of Fig. 3 mathematically transformed into "absorbance" units and replotted.

of one of the standard color mixture curves multiplied by the energy in the corresponding wavelength regions of the spectrum of the sample of radiant energy. If the sample of radiant energy is that reflected from a surface, the spectral composition of the reflected energy is given by the products at each wavelength of the spectral composition of the incident energy and the corresponding radiant reflectance of the surface. This product can be employed as the spectral composition of the reflected energy in the calculation of the tristimulus values of the color of the light reflected from the surface. The integration may be carried out by use of any convenient method of numerical integration (consult appendix).

Lachman, *et al.* (4), ranked dyes in the order of decreasing light stability by improperly using an inadequate abridged selected-ordinate method and the results were stated in "absorbance" units. Furthermore, they failed to establish the validity of the single wavelength type of measurement and their basis of ranking did not take into account the sensitivity of the human eye.

Garrett and Carper (1) determined the color stability of a multisulfa preparation by decanting the clear liquid containing the dye and determining the spectrophotometric absorbance of the dye. While their results and conclusions drawn may be perfectly correct, they nevertheless failed to show that there was a correlation between the dye content *in vitro* and the color of the multisulfa preparation. Since in pharmacy the primary purpose in coloring a product is its total visual effect, then it would seem to be most important to measure color as

perceived, not some other attribute that may or may not correlate with it unless the correlation has been previously rigorously established.

Vickerstaff and Tough (23) discussed the uncertainties of equating fading with the destruction of the dyes involved. They stated that a 50% fade need not involve the destruction of 50% of the dye. The only type of substrate to which such a criterion could be applied with justification is the dyed transparent film, where dye concentrations can be estimated from transmission measurements, and the true reduction in concentration on fading determined.

In another publication of Lachman, *et al.* (5), the comparative light fastness of several water-soluble dyes and their corresponding lakes were evaluated. To make a comparative light stability study of tablets colored with water-soluble dyes and lakes of the same dyes, the concentration of dye in the amount of lake used for the tablets was calculated, and the same quantity of dye was used for the tablets colored with the water-soluble dye. The results of this study indicated that the photostability of the lakes was less than in those of the dyes in the systems studied.

While these results may be correct it should be pointed out that the lakes and dyes were in the tablet formulas in equal dye contents, not equal tinctorial content. The color of the tablets, both before and after fading, is the significant matter, and not the dye contents. Perhaps a more valuable study could have been achieved by starting with the lakes and dyes having the same appearance and then noting their fading with time and light. The *Ciba Review* (15) states, "Perhaps the greatest emphasis should be placed on the recognition that colour is subjective and that colour appearance is not just a matter of spectral absorption and reflection."

Some of the anomalies that have been discussed in the pharmaceutical literature with regard to the light fastness of dyes and lakes varying in different formulations can be, in part, resolved by the following concepts.

Smith and Stead (24) contend that the light fastness of a pigment has no significance and that it is only the light fastness of a pigmentation that can be measured and has any value. In their study they went on to describe the wide differences in light fastness shown by using the same pigment at the same concentration in different media. They further stated: "All that can fairly be said of pigments is that Pigment A used according to Formulation B at Concentration C in Medium D exposed to Light Source E for Time F under Humidity G and Atmospheric Conditions H at Temperature I has a Fastness X relative to an arbitrary standard. This is a *reductio ad absurdum* mode of presenting the idea, but the absurd in this case is strictly true."

Schwen and Schmidt (25) substantiated this in their study. They said: "In the light of present

knowledge it is now quite clear that the system comprising dye and fibre together—or, rather, dye, fibre, and further components—is necessary to define the light fastness of a particular dyeing. One cannot quote the light fastness of a dye alone."

SUMMARY

If those working in the field of pharmacy will realize that it is not the colorants but the color that is the primary objective in coloring pharmaceutical products, then they will be able to take advantage of a vast amount of research that has been done by workers in the fields of textiles, plastics, pigments, dyes, ceramics, films, and paints. The government, through the Bureau of Standards and the Department of Agriculture, has made very basic and rewarding contributions to the science of color. The Optical Society of America and the Inter Society Color Council are just two of the many organizations whose research, when utilized by pharmacy, could put us far ahead of where we are today with regards to the study of color in all of its facets.

To date there has been no study conducted in the pharmaceutical field which treats color as the psychophysical phenomenon that it is. Until this is done all results and conclusions will be open to question.

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