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Review Article

Colorants for Pharmaceuticals

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THE USE of colorants to improve the appearance or other characteristics of pharmaceuticals has been reported in early documents. In many of these, color was closely associated with diseases and their treatment. Since then, the artificial coloring of foods and medicines for various purposes has increased slowly until, in the middle of the 19th century, the discovery of the first synthetic dyestuffs provided the spark which brought into being a rainbow of new colors. Today, as a result of the imaginative research efforts of color manufacturers, a wide range of synthetic organic coloring agents has been made available for numerous industrial uses.

Though a minor consumer of colorants compared to the food or cosmetic industries, pharmaceutical manufacturers have a considerable interest in the use of dyes as colorants. Artificial colors are included in various dosage forms of pharmaceuticals for several reasons. Naturally, one such application is for the purpose of producing an eye-appealing product. Quite apart from esthetic enhancement and consumer appeal, it is often stated that certain colors elicit specific associated effects in some persons. In view of such psychological factors, color is often employed to create related taste responses in a patient prior to the ingestion of a medication. In order to increase the acceptability of various products, an organoleptically compatible color is selected with due consideration for the population group for which the drug is primarily intended.

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Colorants have also been used in pharmaceuticals to conceal or modify undesirable visual impressions which are inherent to a particular preparation. In dosage forms containing active principles resulting from crude drug extraction techniques, differences in the color of the finished product occur as a result of the normal variation between crude drug lots. This point has been recently stressed by Tucker (1) who proposes the use of a color spray drying technique to minimize such differences. In certain tablet dosage forms, small variations in the method of manufacture or physical characteristics of ingredients will produce tablets with varying degrees of whiteness. Syrups and elixirs containing natural flavoring oils also exhibit batch variations in color. Therefore, the addition of artificial colorants provides the means by which a reproducible, uniform appearance of the finished product can be obtained.

Certain drug products contain added color to achieve a desirable cosmetic effect. Preparations for the treatment of skin conditions such as acne may, in addition to their therapeutic ingredients, also contain a skin-tone color to conceal the blemishes caused by the primary condition.

Knowledge gained in recent years has produced a tremendous increase in the use of drugs in veterinary medicine, both therapeutically and prophylactically. These drug products are often marketed by pharmaceutical manufacturers in the form of a "premix" which, prior to distribution to the ultimate consumers, will be mixed by the feed manufacturer with large quantities of animal or poultry feed. Some manufacturers

have colored these premixes artificially to give the feed manufacturer a visual aid in determining whether the medicated premix has been adequately dispersed throughout the finished feed.

One of the most important uses of dyes in drug specialties is for the purpose of identifying the drug in question. With the ever increasing number of drug preparations reaching the market it is readily understandable that any distinguishing feature which enables the physician, pharmacist, and nurse to identify a produce readily is essential medically and toxicologically. The importance of drug identification by color for these reasons has also been recognized by the Food and Drug Administration (2). The expense of special monograms and the limited variations in possible tablet shape also make the coloring of tablets an almost indispensable aid in the identification of drug products.

These several and varied uses of colors in medicinals emphasize the importance of dyes as used by pharmaceutical manufacturers. In the light of recent Food and Drug Administration rulings proposing to delist the great majority of dyes certified for drug use, it is quite clear that a thorough evaluation of the chemical and biological properties of such dyes is an urgent consideration.

CHEMISTRY OF COLORANTS

The current literature on the reactions of dyes in pharmaceutical dosage forms is rather limited as a result of the practice of discarding a dye if its characteristics in a particular system were not satisfactory. Formulators may soon find that they will no longer be able to replace dyes in dosage forms readily when they find that they are physically or chemically incompatible with some component of the composition. Instead, it will be necessary to determine the nature of the offending property and if possible, eliminate it.

Generally speaking, the colorants still available for use in pharmaceuticals can be divided into three major groups: synthetic dyes, lakes and pigments, and natural coloring principles. The basis for the distinction between dyes and pigments is a physical rather than a chemical property, with solubility usually employed as the criterion. Dyes are defined as colorants which are soluble in some commonly available liquid, such as water, alcohol, or oils (3). Those colorants which are essentially insoluble in such liquids or in any medium in which they are designed to be used are classified as pigments.

A specialized area of synthetic pigments of pharmaceutical interest is the class of lakes of the FD&C dyes. These insoluble materials are prepared from certified water-soluble dyes by combination with a basic aluminum or calcium radical and precipitation on a substrate of aluminum hydrate, thus forming an insoluble salt. In addition, there are numerous inorganic pigments such as titanium oxide, iron oxide, etc., which are completely insoluble in organic solvents and aqueous solutions. The constitution, properties, and biological significance of natural coloring principles have been the subject of an excellent review by Mayer (4), although such colors have been largely replaced by the certified synthetic colorants.

Synthetic Dyes.—As the list of certified synthetic colorants for pharmaceuticals threatens to become minimal, a consideration of the properties of those dyes remaining available should be undertaken. First, the properties of an ideal colorant for pharmaceuticals might be contemplated (5). These would include: (*a*) ability to withstand temperatures ranging from 10 to 110° or even higher, (*b*) must be stable within a pH range of 2–9, (*c*) must be stable to light over long intervals of exposure, (*d*) should be available in both an oil-soluble and water-soluble form, (*e*) should blend well with other colorants in various systems, (*f*) should resist oxidation and reduction, (*g*) color strength should be capable of standardization so that there is no batch to batch variation, and (*h*) the necessity of being without suspicion of carcinogenic activity.

Although there are currently no dyes that fulfill all of the above, many of these criteria can be met. Information concerning the chemical structures and physical properties of the certified dyes are available from numerous sources (5–13). In a paper prepared for the Perkin Centennial, Zuckerman (12) has discussed the structure and properties of present day certified colorants. From a chemical standpoint the certified FD&C colors fall into five classes: azo, triphenylmethane, indigoid, xanthene, and pyrazolone.

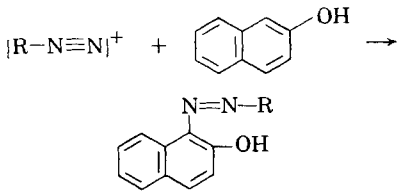
Azo dyes, however, comprise almost 90% of the total volume of certified colors used. A knowledge of their chemical structure can be employed to predict, to a fair degree, the physical properties of these colorants. The general formula for an azo dye is

$$R_1—N{=}N—R_2$$

R_1— is any aryl group

R_2— is a phenol, amine, or other group capable of coupling to a diazonium salt

The general coupling reaction involved in the formation of the finished dye would be (8)



Inskeep and Kretlow (14) have illustrated, in great detail, the general procedures for the preparation, purification, and blending of certified dyes of the azo type. The batch operation is carefully described in a flow sheet as well as through the use of structural formulas. It is pointed out that the presence of water solubilizing groups such as SO_3Na, COONa, and, to a lesser extent, the OH group, whether substituted on the diazonium component or the coupling component, increases the water solubility of the dye molecule. The absence of these groups gives molecular structures which exhibit true oil solubility. The manufacture of colorants of certified purity is a highly specialized branch of the dyestuff industry because extraordinary precautions and controls are necessary to eliminate objectionable side reaction products and metallic or other impurities. For example, the maximum amounts of lead and arsenic permissible are 10 and 1.4 p.p.m., respectively, in the FD&C colors and 20 and 2 p.p.m. for the D&C and Ext. D&C colors (15). The water, acids, alkalies, solvents, and intermediates used must all be the purest obtainable.

As noted by Zuckerman (12) the specific properties of a dye, such as fastness and chemical behavior, depend largely on the substituent groups. These groups are of two kinds: the chromophoric groups and the auxochromic or salt-forming groups such as the acidic or hydroxyl group. The chromophoric groups determine the chemical class to which the dye belongs and its oxidation or reduction potential. The auxochromic groups are largely responsible for the coloring properties and the action toward acids, alkalies, and light. An additional function of an auxochromic group is to stabilize the molecule so that the new molecular configuration has a greater resonance stabilization than the unsubstituted compound. This stabilization causes absorption in the longer wavelengths and results in a deepening of the color. Changes in dyes consisting either in complete or partial loss of color may occur for several reasons, which will be discussed under the heading of stability.

Since it is impossible to produce synthetic dyes commercially which consist of a single chemical entity, the importance of definitive analytical methods for the determination of these dyes is self-evident. The well established methods for the analysis of certified colors are given in "Official and Tentative Methods of Analysis of the Association of Official Agricultural Chemists" (16). However, incomplete and side reactions during synthesis normally produce substances other than the principle component. Also, certain extraneous materials may be introduced during the process of isolation of the pure dye. Research conducted in the color laboratories of the U. S. Food and Drug Administration as well as in the laboratories of dye manufacturers has established for the majority of FD&C colors: (*a*) their chemical structure, (*b*) the identity of the isomeric and homologous colors, and (*c*) the identity of colorless organic constituents.

As a result, rapid and accurate methods for the quantitative analysis of all organic constituents expected to be present in a dye are now available. This then permits interested regulatory agencies to describe each color accurately and to determine whether each batch submitted for certification is equivalent to the reference standard material previously approved.

Jones, *et al.* (17, 18), were able to separate and determine the pure dye content of samples of triphenylmethane colors by a stepwise synthesis and analysis of all components of all products of the reactions. They were further able to differentiate each of the isomers of all of the various dyes by a variable reference technique (19).

Several investigators (20–30) have isolated and identified intermediates produced in the preparation of FD&C dyestuffs. In particular, the work of Link (20) presents a general procedure by which dyestuffs can be examined for the presence of uncombined intermediates. The procedure involves a chromatographic separation followed by a spectrophotometric identification of the uncombined intermediates. A technique for the purification of FD&C Red No. 2 suitable for use as an analytical reference standard was also described by Link (21). Methods suitable for the detection of six subsidiary colors in FD&C Red No. 2 are also presented.

Jones, Harrow, and Heine (28) undertook a thorough investigation of the composition of FD&C Blue No. 2. This color is prepared commercially by sulfonating indigo. Each of the possible symmetrical sulfonated compounds was prepared in addition to various disulfonated products and a chromatographic method of

separating many of the products was developed. A spectrophotometric method which was developed was found to be a much more precise method than titration with standard titanium trichloride for determination of pure color in FD&C Blue No. 2.

Of the FD&C colorants, the one distinct chemical class remaining is found in FD&C Red No. 3, an iodofluorescein derivative. A thorough study of a closely related series, the bromofluoresceins, was conducted by Graichen and Molitor (29) in 1959. It can be expected, however, that the chemistry of the iodofluoresceins is practically identical with that of the bromofluoresceins. A total of at least 10 halogenated products theoretically could be expected under the conditions employed for the iodination of fluorescein.

Thus, information is now available on the chemistry of the certifiable color additives and their subsidiary products formed through secondary reactions. This information should be expected to contribute materially to the clarification of legislation designed to evaluate certifiable color additives of the FD&C series.

Pigments and Lakes.—Approval by the Food and Drug Administration in 1959 of certified lake pigments for pharmaceutical uses has considerably enlarged the utility of this class of colorants. Previously, only titanium dioxide, purified carbon black, and carmine were approved by the FDA for food, drug, and cosmetic use. This development results in a significant step forward for the pigment field. The general manufacturing details of pigment preparations, together with their properties, have been reviewed by Anstead (31). He also includes a summary of the requirements of colors for cosmetics including aspects of relevant legislation in Great Britain and the United States.

An excellent review of the chemistry and physics of organic pigments is provided by Pratt (34). Of particular note is a special chapter in which emphasis is placed on a new interpretation of the significance of physical structure of pigments as related to color. This factor is of fundamental importance in the use of nondissolved materials. With dyestuffs, consideration of the relationship between color and structure has been largely restricted to the basis of chemical or molecular structure. In pigment technology, in addition to chemical properties, a study and measurement of particle size and shape, aggregation, molecular space relationships, and surface conditions are essential for total understanding and utility of these materials. As there are many applications for these materials in the food, drug, and cosmetic fields, Powers (9) encouragingly states that inorganic pigments have excellent light fastness and complete insolubility in solvents and aqueous solutions. He notes that the most important pigments are the iron oxides, chrome oxide greens, ultramarine blues and pinks, and the carbon blacks. A summary of the properties of the above is supplied. Mattiello (11) has compiled a book describing the chemical compositions, manufacturing processes, properties, uses, and methods of identification of pigments. The various chapters have been written by recognized authorities in the field of protective coatings and pigments, with each section being prefaced by an excellent brief theoretical discussion.

Zuckerman (32) briefly describes the use of lake colors in and on food products and notes that application will surely be found in many areas in addition to their use in foods. Lake colors are odorless and tasteless and are resistant to migration due to their insolubility. Jablonski (10) has reviewed the use of pigments and lakes in food products. He notes that until recently only lakes prepared from animal or vegetable coloring matters achieved widespread usage. With the exception of the use of titanium dioxide in tablet coating, reports on the use of pigments in lakes in pharmaceutical products are sparse. Tucker and co-workers (33), however, have reported on tablet color coating with pigments.

With few exceptions the natural organic coloring matters find little use in the pharmaceutical field. A comprehensive review of the significant chemical and physical properties of the natural colorants is supplied by Mayer (4). Various authors (6, 9) have commented briefly on their use in the drug field and summarized their application properties.

STABILITY OF COLORANTS IN PHARMACEUTICAL SYSTEMS

Although the use of synthetic dyes for imparting color to medicinals is obviously widespread in the pharmaceutical industry, investigations into the stability and stabilization of colors in these products have, until recently, received little attention by pharmaceutical researchers. With a few notable exceptions, the literature on the use of colorants for pharmaceuticals is so scattered and incomplete as to offer little assistance to a worker in the field of color stability as far as industrial application is concerned. The photosensitivity of these dyes, when incorporated into various formulations, represents a formidable

problem. Though this is a generally recognized difficulty, a conspicuous lack of information still exists in the pharmaceutical literature concerning the influence of light and heat on color fastness. This lack of data can be ascribed to several factors, among which are: (*a*) the unavailability of a suitable exaggerated light stability cabinet, (*b*) the unavailability of appropriate analytical techniques for measurement of color changes under the various circumstances, (*c*) the common practice of discontinuing the use of a specific color when found unsuitable in a given formulation without determining the nature of the objectionable characteristics, and (*d*) the treatment of such data as confidential within a particular company.

Aspects of Photostability.—Approaches to predicting the stability of colorants have been based on both chemical and physical measurements. Since the principle mode of reduction of color intensity results from photochemical reactions, interested individuals have attempted to utilize various exaggerated light testing techniques in an effort to predict the degree of photosensitivity of dyes contained in their products. However, although it is known that tests of this nature have become more prevalent, few reports exist in the pharmaceutical literature concerning their use. This may be attributed to the fact that the methods employed were not completely satisfactory or were highly specific (35). Experiments performed by Arny, *et al.* (36, 37), disclosed the effects of sunlight and diffused light on various pharmaceutical ingredients when stored in several types of glass containers. Of all the commercially available glasses studied, the authors found that amber glass afforded the greatest protection.

Although there is some lack of information concerning the photostability of pharmaceuticals, there appears to be an abundance of data available on the influence of light on textiles, dyes, and pigments (38–47). The necessity of having a standard light source is well recognized in these fields.

The most readily available source of radiant energy is sunlight, but Hadfield (47) has thoroughly delineated the unsuitability of sunlight or daylight as a source of light in testing color stability. He points out that the radiation received from the sun is subject to wide variation both in total intensity and in distribution of energy. Because of this, exposure tests to sunlight result in marked differences in relative effect for samples exposed to this light source. It has been reported by Appel and Smith (43) that by limiting the exposure of samples to between 9 a. m. and 3 p. m. on clear days, the low intensity radiation and high atmospheric humidity occurring at intervals during continuous exposure is avoided. This, they indicate, yields data that have been shown to be generally reproducible at different times of the year and in different parts of the United States. Despite the above efforts at standardization of sunlight exposure, the findings of other investigators appears to be at variance with the findings of Appel and Smith.

Attempts to measure the energy of the sun's rays and to make exposures for a definite number of energy units were inadequate in that the following factors were not taken in consideration: (*a*) variation of sun intensity from season to season and area to area, (*b*) daily cycles of change in temperature and humidity, (*c*) variations in spectral character of radiation during time of exposure, and (*d*) the presence of atmospheric impurities (48). In an endeavor to concentrate the sun's rays and thereby decrease the time required for fading exposure, lenses were utilized, though unsuccessfully, because of the excessive heat developed (49). In order to control, diminish, or eliminate the effect of these variables, various artificial light sources have been developed with a spectral energy distribution intended to simulate that of direct sunlight. Sources such as carbon arcs (50, 51), mercury vapor lamps (52), fadeometers (39, 41, 44), and tungsten filament lamps (42, 45) have been used to determine the light stability of colored textiles, dyes, and pharmaceuticals susceptible to photochemical reaction.

Since most pharmaceutical preparations are usually stored in retail pharmacies, storage areas of a warehouse, homes, hospitals, and doctors' offices, the amount of light in the ultraviolet spectrum of sunlight that penetrates through the glass store front or window panes is substantially decreased because of absorption by the glass. Husa (58) indicated that ordinary glass absorbed the shorter ultraviolet light as well as the longer infrared found in sunlight. This would suggest that the decomposition caused by sunlight passing through glass would be due to visible light and/or the ultraviolet and infrared rays which are nearest in wavelength to visible light.

In a report by Esselen and Barnby (59), light intensities outside and inside retail stores were measured and compared. The data obtained indicate that the outdoor readings were over 400 times the average reading taken on typical store shelves exposed to light of normal intensity.

Pharmaceutical products are very seldom exposed to direct sunlight and when they are, it is for a relatively short period of time. As a result, it was felt that a high intensity light source which would closely simulate ordinary room illumination would be more suitable for the study of dosage forms (35). This type of light source should approximate more closely the light falling on products kept in usual storage areas. Several studies to be discussed subsequently employed the above-mentioned light source as a standard for testing.

Cabinets for housing a suitable light source, whatever its nature, are available in a multiplicity of designs. Numerous patents (53–57) have been issued for various installations depending upon the desired end use. The basic design consists of a housing to contain the sample at a fixed distance from a light source. In some instances provisions are made for humidity and/or temperature control while, in other cases, only the character of the radiation is regulated. The degree of control varies with the intended end use of the data obtained but, in almost all situations, an attempt is made to extrapolate the information derived to some extended time interval.

Chemical and Physical Stability Considerations.—Certain general statements can be made about the chemical and physical behavior of certified colorants in pharmaceutical systems. Changes in dyes resulting either in complete or partial loss, or in alteration of color, may occur for several reasons. Some of the more common causes for the color change are exposure to light, the action of oxidizing or reducing agents, and the action of acids or alkalies. Peacock (7) has tabulated data on the resistance of the certified colorants to a wide range of reactive agents and conditions. The summary gives an indication of dye resistance to sunlight, to organic and inorganic acids, alkalies and some metallic salts, and to oxidizing and reducing conditions.

Inskeep and Kretlow (14) have also summarized the relative stabilities of the FD&C colorants. They note that the degree of fastness of various synthetic dyes may vary with the dye itself, the nature and intensity of light, the amount of moisture present, and the vehicle in which the dye is employed. They have presented the following general information:

"*A common property of dyestuffs is their ability to take up hydrogen with the formation of colorless compounds. In nitro and azo dyes, amino compounds are produced, whereas other classes are converted into so-called leuco-compounds which contain two more atoms of hydrogen than the original dye from which they are derived. They are reconverted into the original dye on oxidation.*

"*Most of the certified colorants are very unstable in the presence of reducing agents. The same is true in the presence of oxidizing agents, although the red colors are slightly more stable than the others. The most common type of reduction encountered in the use of FD&C colors involves the action of a metal such as tin or iron in an acid medium. The acid acts on the metal, liberating hydrogen, which in turn reacts with the dye, to bring about a reduction. The result is a loss of color.*

"*The certified colorants vary considerably in their action towards acids and alkalies. FD&C Blue No. 2, for example, fades rapidly in an acid medium; FD&C Red No. 3 is completely precipitated and should not be used in any product where acid is present. The azo dyes are comparatively stable in weak acids, but some of them should not be used in a basic environment.*"

Evenson (60) has studied the effect of light on FD&C Red No. 3 and D&C Red No. 21. His study has shown that the addition of small amounts of FD&C Blue No. 2 greatly accelerates the fading of FD&C Red. No. 3 in solutions. As a result, he points out that care should be taken to select mixture components of approximately equal resistance to light, if possible.

Several studies involving pharmaceutical systems have been reported by Lachman and colleagues (61–66). One such investigation was conducted in an effort to determine the light stability of 10 certified water-soluble dyes when used in tablet dosage forms (62). No effort was made in the study to elucidate the specific fading mechanisms of the several colors; rather, an attempt was made to determine the relative stability of the colors under normal and exaggerated illumination. The relationship between fading and dye structures as well as fading and light intensity was discussed. The extent of dye fading beneath the surface of the tablet was also measured. The authors concluded that the fading rate is most rapid during the initial stages of irradiation. Of significance is the observation that the exaggeration of color fading produced by the intensified illumination source employed did not follow a particular pattern for the dyes studied.

In another study using identical exaggerated lighting conditions, Lachman (63) evaluated the relative light fastness of several water-soluble dyes and their corresponding lakes. Employing initial fading rate constants as criteria for de-

termining light fastness, the lakes studied exhibited less photostability than the dyes in the tablet systems studied. As an example of the variations in data that may result when different lighting systems are employed for exaggerated testing, Tucker (33) reported that enhanced light stability resulted from the use of lakes as colorants for pan coated tablets. There are no established standardized conditions for light stability testing in the pharmaceutical industry, and correlation of data is hardly possible. Thus, literature reports such as the aforementioned pair must necessarily be treated individually. It must also be remembered that the lakes were applied, in one instance, in conjunction with pan coating techniques and, in the other case, the lakes were blended directly into a granulation prior to compressing tablets.

In another study the influence of temperature and pH on the surface color and total dye content of tablets colored with certified dyes was investigated (66). Samples of tablets colored with three dyes and buffered at several pH levels were stored at elevated temperatures and tested for both residual dye content and surface fading. The results of the study disclosed no relationship between the fading at the surface of the tablets and the actual loss in colorant concentration at elevated temperatures.

The same authors have also evaluated the effect of ultraviolet absorbers on the photostability of colored tablets (65). These studies were performed under light sources simulating the spectral energy distribution of sunlight and normal and exaggerated room illumination. The use of the ultraviolet absorber was most effective against color fading in tablets exposed to simulated sunlight. Signore and Woodward (67) studied the stabilizing effects of ultraviolet absorbers such as 2-hydroxy-benzophenone derivatives on dyes in solution. They found that significant protection was afforded to selected dyes in 50% ethanol solutions irradiated in the presence of low concentrations of U.V. absorbing materials. However, U.V. absorbers do not universally protect all dyestuffs in solution as has been illustrated in papers by Hardy and Coleman (68) and Gantz and Sumner (69).

The protective influence of glass of various spectral transmission characteristics on the light-induced fading of colored tablets has been investigated by Swartz (64). The apparent rates of fading of the tablets irradiated through the various glass samples were determined following exposure of the tablets to intensified fluorescent illumination.

The observation that common pharmaceutical materials may react with dyes to promote fading in solution prompted Scott, *et al.* (70), to investigate the color loss of certified dyes in the presence of nonionic surfactants. The retention of color in aqueous buffered solutions containing certified dyes and nonionic surfactants was measured after 14 days storage at elevated temperatures. In all but four of the 30 systems examined, accelerated fading was noted over that obtained with solutions of the dye alone. The intensity of this effect was found to vary from one dye-surfactant system to another and was not generally predictable. Kuramoto and co-workers (71) determined the stability of FD&C Blue No. 2 in a buffered aqueous solution in the presence of several commonly employed pharmaceutical materials. They found that sugars such as dextrose, lactose, and sucrose increase the rate of fading, whereas sugar alcohols such as mannitol and sorbitol do not appreciably affect the rate. Numerous antioxidants were also tested in the system and found not to appreciably retard the fading. By means of phase studies using cloudpoint titration techniques, Lachman (72) studied the interaction between several quaternary ammonium compounds and certified dyes. It was demonstrated that three commonly employed cationic surfactants formed insoluble complexes with FD&C Red No. 1, FD&C Blue No.1, and D&C Yellow No. 10. Although the report was limited to data on only three certified dyes, the same phenomenon was found to occur with several other dyes.

Another study concerning itself with the mechanism of color fading in pharmaceutical formulations was presented by Garrett and Carper (73). This paper reported on the color stability of a liquid multi-sulfa preparation by kinetic investigation of the thermally accelerated degradation of the color. The colorant employed was a combination of FD&C Yellow No. 6 and D&C Red No. 33. The authors did not attempt to determine the actual mechanism of the reaction of the ingredients which were responsible for fading. They were principally interested in predicting the extended shelf color stability of a formulation in a brief period.

Though of less immediate value to workers in the pharmaceutical sciences, numerous reports have appeared in the literature of the textile and paper processing industries concerning dye stability. A group of the more pertinent of these will be commented upon in the following paragraphs.

A study of the oxidation of the azo dyes and

its relationship to light fading was carried out by Desai and Giles (74). They employed various oxidizing reagents including ceric sulfate, potassium dichromate, and hydrogen peroxide to disrupt the azo group in an effort to find if any correlation exists between resistance to oxidation and light fastness on textiles. However, following extensive experimental trials, the authors concluded that it seemed unlikely that a chemical agent could be found to fade dyes in the same manner as light exposure and thus be suitable for a rapid and reproducible screening test.

Atherton and Seltzer (75) attempted to correlate the fastness of dyes in cellulose acetate films to dye properties when deposited on textiles. They based their experiments on measurements made over the initial stages of the reaction in order to minimize the possibility of reactions between the dye and its decomposition products. The light source employed was an enclosed carbon arc projector. A series of simple monoazo dyes were selected because of their ease of synthesis, low light fastness, and colorless decomposition products. The results of these experiments did not permit the correlation hoped for. However, the workers were able to determine the influence of the chemical nature of substituent groups and their position relative to the azo linkage on the light fastness of the parent compound. This permitted them to propose a relationship between chemical structure and order of light fastness of these dyes under the specific conditions studied.

Other authors attempted to determine the influence of the substrate on the light fading of azo dyes and the influence of the physical state of the dyes upon their fastness properties in dyed textiles (76–79). Following a review of the data in every instance, only very limited correlations were possible. Desai and Vaidya (80) studied the action of light on certain triphenylmethane dyes, and by the use of both chemical and spetrophotometric methods were able to determine the photodecomposition products. They further showed that the same photochemical changes take place when the dyes are exposed to the action of different light sources. Various aspects of the fading of colored materials as a result of temperature, humidity, and light have been reviewed by Cunliffe (81), Morton (82), Taylor and Pracejus (83), and Barker (84). A review of the mechanisms of the free radical reactions which might take place in photosensitized oxidations of colorants in solutions has been reported by Weiss (85).

Rather than base the effects of light on dyes in solution on a systematic accumulation of practical data as has been done above, Bowen (86) has attempted to apply theoretical concepts in photochemistry to help clarify mechanisms in fading reactions. He has noted that many of the photo reactions of dyes have been interpreted as "electron transfer" reactions and suggests that experiments to elucidate some of the following properties would be helpful: "(*a*) precise measurements of the effects of oxygen (even in traces) on the photochemical change; (*b*) similar measurements with deliberately added oxidizing and reducing agents; (*c*) determinations of the temperature coefficient of photochemical reactions, without and with air present, to throw light on the nature of the processes limiting the efficiency; (*d*) examination of the effect of moisture on the reactions, in case liquid diffusion of substances should control the rate; (*e*) precise work on the detailed shapes of absorption bands of dyes both in solution and solid systems which might lead to a fuller understanding of the nature of the light absorbing process."

A more complete knowledge of the above should permit the active application of theory to the photodegradative processes of dyes.

APPLICATION PROPERTIES OF COLORANTS

It has been pointed out earlier in this report that quantitative data on the light and thermal stability of the certified dye is not readily available in published reports. Nevertheless, some information can be obtained from general reviews prepared by the various dye manufacturers (3, 6, 7) but these data are only qualitative in nature. Scott (70) has observed that the interactions between dyes and other pharmaceutical reagents leading to poor color stability in finished products have received little attention.

An excellent bibliography on color matching and its practical aspects has been prepared by Peacock (87). Color matching in the cosmetic industry is discussed by Stearns (88) who concludes that "color matching is very definitely an art, and the man who does color matching of cosmetics must be a highly skilled artisan." To give credence to this he states that there are 32 important factors involved in the judging of color effects, all interacting to various degrees.

The solubility properties of certified dyes are discussed in numerous trade articles. Upon observation of these values, variations in results that cannot be attributed exclusively to experimental error are sometimes found. Zuckerman

(89) determined that the maximum solubility of the dyes, at constant temperature, varied with with the quantity of excess solute and proceeded to develop a procedure for determining the maximum solubility of all the water-soluble FD&C colorants based on this.

An excellent review entitled, "Colour and Its Measurement" (90) has summarized many newer instrumental techniques of color measurement as applied to the textile industry. The bibliography contains 45 references in the general field of color perception, color application, and measurement.

THE REGULATION OF COLOR ADDITIVES

Following the discovery of mauve in 1856 by Sir William Perkin, the development of available colors with varied hues increased rapidly. For many years little attention was paid to the toxicology of these substances but by 1900 Congress was ready to appropriate funds to enable the Secretary of Agriculture to investigate the nature of "coloring matters" in order to establish the principles enabling their safe use in foods, drugs, and cosmetics. Before the passage of the Federal Food and Drug Act of 1906, seven colors were accepted as harmless and a voluntary system of certification based upon physiologic tests was set up. During the 32 years which elapsed before the new Food, Drug, and Cosmetic Act replaced the 1906 law, an additional 15 colors were certified for food, drug, and cosmetic use.

The 1938 Act provided more extensive and elaborate provisions for regulating the use of color additives with tests for toxicity, purity, stability, and local irritation. It also required that the structure of certified colors must be known and the purity determined by appropriate analytical methods. Certification was now divided into three classes: FD&C colors for foods, drugs, and cosmetics; D&C colors for drugs and cosmetics, and Ext. D&C colors for external use only.

Under the powers granted the FDA, decertification of previously approved colors has become increasingly frequent in recent years as more intensive pharmacological testing was applied to these substances. In addition, attitudes resulting from the controversy involving the safety of food additives were reflected in an increasingly critical and cautious attitude toward the use of color additives. In a report discussing Bill S2197 (Color Additive Amendments of 1959) Senator Hill (91) urged the replacement of the previous color additive regulations with the new "sound and uniform system for the listing of color additives of any kind which may be safely used in foods, drugs, or cosmetics subject, when necessary, to appropriate tolerance limitations and other conditions of use. . . ." Senator Hill was emphasizing the importance of the tolerance provision as an answer to a Supreme Court decision which defined the "harmless" principle (of the 1952 Act) as meaning harmless regardless of the quantity of the coal-tar color which is being used.

Williams (92), in analyzing from a legal point of view the color additive bills submitted to Congress, showed concern for the hazards associated with the procedures for listing and exempting safe color from certification. The absence of a practical jurisdictional test which would exclude from the statute colors known to be harmless contributed a burdensome character to the procedural requirements of the proposed legislation. Schramm (93), in a similar review of the bills before Congress in 1959, stated that the basic principles involved in these bills met the approval of the Certified Color Industry Committee. An objection of the Committee to the mandatory requirements for analytical methods as a condition for listing a color additive was resolved in the Senate bill on the basis of an industry and Department of Health, Education, and Welfare discussion. The Committee also objected to the specific inclusion of cancer since there was no logical reason to separate this pathology from other adverse physiological effects. Dohl (94), in discussing the proposed bills from the point of view of the pharmaceutical industry, while objecting to the Delaney Cancer Clause and to several less important aspects of the legislation, nevertheless supported the Senate bill as better than no legislation at all. Similar support, including the reminder that the pharmaceutical industry is accustomed to control, came from Goodrich (95).

On July 12, 1960, the Color Additive Amendments of 1960 became law and, following the expiration of a transitional period, all colors will become subject to uniform statutory rules. The disappearance of the term "coal tar colors" will not be mourned while its more inclusive replacement "color additives" must still find its place in the everyday vocabulary of pharmacy and the pharmaceutical industry. A section by section analysis of the new law has been published and should be very helpful to those responsible for conformance with the provisions of the law (96). Briefer commentaries (97, 98) reviewing the overall significance of the law have also made their appearance in literature.

Failure of the pharmaceutical industry to demonstrate the safety of D&C colors by 1963 will result in automatic decertification of these colors unless an extension is granted on the basis of studies initiated but not completed before the deadline. Many product development pharmacists and control chemists are of the opinion that permissible FD&C colors are inadequate for all pharmaceutical requirements. It is necessary to recognize the fact, and many pharmaceutical executives have not done so, that eliminating the use of colors in tablets, syrups, elixirs, etc., will not necessarily provide uniform, colorless, products. Variations in raw materials and intermediates are difficult or costly to control and lack of product uniformity will undoubtedly engender complaints. Significant protection against change in product appearance due to aging could also be provided by suitable coloring agents. The new color additives law regulates the production of pharmaceuticals in an important way and industry may find it advisable to invest in the acquisition of scientific information in order to assure compliance.

A remarkably thorough compilation and review of legislation regarding the available colorants for use in most of the nations of the world has been assembled by J. PlaDelfina (99, 100). In addition, this comprehensive report discusses the chemical structure and reactivity, toxicology, and pharmaceutical applications of all colorants available for both internal and external use. The review is appended by a series of outlines in the form of a catalog which summarizes and also completes the text making it useful for those not very familiar with the field. The six-column summary lists the chemical classification and structure, commercial and legal aspects, as well as pharmacologic data on all the material cited in the paper.

CONCLUSION

Research pharmacists and others concerned with the formulation of pharmaceutical products and the avoidance of confusion and errors in manufacturing and dispensing are dismayed and alarmed at the nonchalance with which many scientists and executives in the pharmaceutical industry have accepted recent decisions involving the decertification of important colorants. Any degree of reflection on the realities of a situation permitting only "colorless" or "naturally colored" pharmaceuticals, as has been blithely proposed by some, would bring into focus a host of new problems of disturbing significance. It is impossible to conceive of responsible individuals experienced in the development of pharmaceutical products who would solve problems at the expense of present or potential risk to patients. Scientists should, however, be prepared to fight off ill-conceived decisions based upon unknown fears or political advantages.

In spite of the lengthy history of the use of colorants in pharmaceuticals, a review of the literature brings out the fact that relatively little attention has been given to investigations of the behavior of colorants in pharmaceutical systems. Basic studies are needed in the field of chemical reactivity of colorants with other components of medications, the stability of individual or mixed colorants in varying environments, and the relative toxicity of color additives. As with all substances entering into biological systems, it is necessary to relate the quantity of agent administered with the response. Toxicology, like pharmacology, is dependent upon posology.

As is evident from this review, the research pharmacist planning investigations of the physical and chemical properties of colorants can lean upon the experiences of scientists in other fields whose experiments have yielded knowledge applicable to the use of such substances in drugs. The basic chemistry of dyestuffs, the application properties of colorants, and instrumentation for measuring color and color changes have been probed with concentrated intensity by workers in food processing, textiles, photography, and protective coating. The fruit of their labors provides a solid foundation for the development of needed knowledge in the formulation of pharmaceuticals.

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