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Review Article

COLORANTS - THE COSMETICS FOR THE PHARMACEUTICAL DOSAGE FORMS

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ABSTRACT

Colorants are mainly used to impart a distinctive appearance to the pharmaceutical dosage forms. There are many types of pharmaceutical formulations which need to be colored such as tablets, tablets coatings, capsules (hard gelatin, soft gelatin), liquid orals, tooth pastes, ointments and salves etc. The purpose of coloring varies with different formulations. Coloring may be required to increase the aesthetic appearance or to prolong the stability or to produce standard preparations or for identification of a particular formulation. Color psychology says that, the color of the product may also influence the efficacy of therapy. Thus, the prime priority of colorants is to increase the aesthetic appearance of the product, so we can say that the colorants are the cosmetics for the pharmaceutical formulations. The classification of various colorants including FD&C categories, the lists of colorants and their uses, the description about major colorants widely used in the formulations was discussed here in detail. In many regions around the world there is a distinction between colors that may be used in drugs and those for food use. This review also discusses the Status of color additives based on Code of Federal Regulations, The international regulatory status, Coloring systems for various dosage forms, Colorant blending, Handling precautions, Safety, Stability and Storage data of various colorants. Legislations, which govern the usage of colorants, include European Union Legislation and United States Legislation.

Keywords: Colorants, Coloring agents, FD&C colors, Pharmaceutical Colorants and Coloring systems.

INTRODUCTION

Colorants or coloring agents are mainly used to impart a distinctive appearance to the pharmaceutical dosage forms. We can also say that the colorants are the cosmetics for the pharmaceutical preparations, because the aesthetic appearance of dosage forms can be enhanced by using suitable colorants. The main categories of dosage form that are colored are: tablets (either the core itself or the coating.), hard or soft gelatin capsules: (the capsule shell or coated beads), oral liquids, topical creams, toothpastes, ointments and salves. The elegance and eye appeal of a colored product is valuable, especially for children whom it is often used to treat with syrups, tablets, or capsules, to avoid injections and allow treatment at home.

Pharmaceutical preparations are colored mainly for following reasons:

Increases acceptability

Unattractive medication can be made more acceptable to the patient by the use of color, and color can also be used to make a preparation more uniform when an ingredient in the formulation has itself a variable appearance from batch to batch. Many patients rely on color to recognize the prescribed drug and proper dosage. These attributes assist in improving patient compliance[1].

It is believed that brightly colored tonics, cherry red children's cough mixtures and flesh-tinted powders and ointments are more likely to be used because they are attractive.

For identification

It helps to identify a product in its manufacturing and distribution stages. Colors may be used for identifying similar-looking products within a product line, or in cases where products of similar appearance exist in the lines of different manufacturers[2]. The use of different colors for different strengths of the same drug can also help eliminate errors. A specific example is the anesthetic Trichloro ethylene, which may be colored blue to distinguish it from chloroform which it resembles in physical characteristics.

Coloring may help a doctor to recognize a previous treatment. Specific colored products become known to doctors and pharmacists, and this can help sales[3].

Standard preparations

Natural calamine is obsolete for pharmaceutical purposes, because it is not constant in color and has been replaced by artificially prepared material tinted with a form of ferric oxide. Differences in the tint of green soft soap caused by variation in the quality of the oils used in its preparation are sometimes covered by a suitable dye. When lactose is used as the diluent for powdered opium it should be colored with Caramel to give a uniform appearance to the product[3].

Stability purpose

Some of the insoluble colors or pigments have the additional benefit when used in tablet coatings or gelatin shells of providing useful *opacity*, which can contribute to the stability of light-sensitive active materials in the tablet or capsule formulation. Pigments such as the iron oxides, titanium dioxide, and some of the aluminum lakes are especially useful for this purpose[4].

COLOR PSYCHOLOGY - THE PSYCHOLOGICAL EFFECTS OF COLOR

The study of color is complex, and made difficult by its variety of systems, which include the aesthetic, psychological, physiological, associative, and symbolic. This has led to discoveries of the psychophysiological attributes of color[5]. Color psychology says that the color of the product may also influence the efficacy of therapy. Color effects have universal meaning.

Colors in the red area of the color spectrum are known as "warm colors" and include red, orange and yellow (Fig.1). These warm colors evoke emotions ranging from feelings of warmth and comfort to feelings of anger and hostility. Colors on the blue side of the spectrum are known as "cool colors" and include blue, purple and green. These colors are often described as calm, but can also call to mind feelings of sadness or indifference[6]. The studies were also applied to medications.

Ideal properties of a colorant

- Nontoxic and have no physiological activity. Free from harmful impurities
- Is a definite chemical compound because then only its coloring power will be reliable, its assay will be practicable and easier.
- Its Tinctorial (coloring) power should be high so that only small quantities are required.

- Unaffected by light, tropical temperatures, hydrolysis and micro-organisms and, therefore, be stable on storage[7].
- Unaffected by oxidizing or reducing agents and pH changes.
- Compatible with medicaments and not interfere with them.
- Ready solubility in water is desirable in most cases but some oil-soluble and spirit-soluble colors are necessary.
- Does not interferes with the tests and assays to which the preparations containing it are subject. Should not be appreciably adsorbed on to suspended matter.
- Free from objectionable taste and odour.
- Readily available and inexpensive.

Natural coloring matters are less satisfactory than coal tar colors in many of these respects.

Classification

A. Organic dyes and their lakes

B. Inorganic or mineral colors

C. Natural colors or vegetable and animal colors

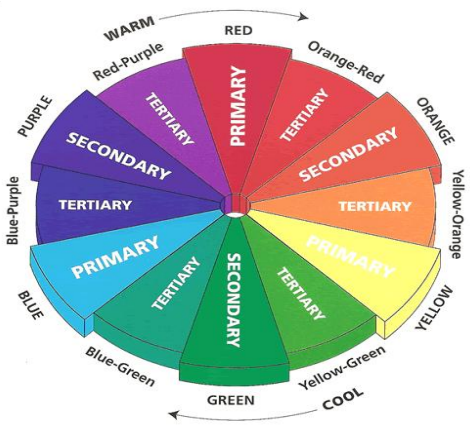

Fig. 1: Color wheel

Organic dyes and their lakes

Dyes

Dyes are synthetic, chemical compounds that exhibit their coloring power or tinctorial strength when dissolved in a solvent[8]. They are usually 80 to 93% (rarely 94 to 99%) pure colorant material. Dyes are also soluble in propylene glycol and glycerin. They are available in a wider range of shades or hues with higher coloring power than the natural pigments. Dyes are usually cheaper in cost.

The physical properties of dyes (particle size, variation in the grinding and drying process, different suppliers) are usually not critical in terms of their ability to produce identically colored systems. The tinctorial strength of a dye is directly proportional to its pure dye content. Solutions of dyes should be made in stainless steel or glass-lined tanks (for minimization of dye- container incompatibility) with moderate mixing and should routinely be filtered to remove any undissolved dye particles[9]. Colors for clear liquid preparations are limited to the dyes. Examples include Tartrazine, Erythrosine, Sunset Yellow and Patent Blue V.

Lakes

Lakes have been defined by the FDA as the "Aluminum salts of FD&C water soluble dyes extended on a substratum of alumina". Lakes prepared by extending the calcium salts of the FD&C dyes are also permitted but to date none has been made. Lakes also must be certified by the FDA. Lakes, unlike dyes, are insoluble and color by dispersion. Consequently, the particle size of lakes is very critical to their coloring capacity or tinctorial strength (Table 1). Generally, the smaller the particle size, the higher the tinctorial strength of lakes due to increased surface area for reflected light. Lakes are formed by the precipitation and absorption of a dye on an insoluble base or substrate. The base for the FD&C lakes is alumina hydrate. The method of preparation of the alumina hydrate and the conditions under which the dye is added or absorbed determines the shade, particle size, dispersability as well as tinctorial strength. Other important variables are the temperature, concentration of reactants, final pH, and the speed and type of agitation. The shade or hue of a lake varies with the pure dye content.

The use of insoluble certified lakes has several advantages, namely:

- The fact that they are insoluble enables the drying stages to be performed more quickly.
- Mottling is reduced because the opacity of the system minimizes the defect of tablet surface depressions.
- Over coloring is not a problem because the system is opaque, hence, only one shade of color will result.
- Full color development can be achieved with a fewer number of application states. This results in significant time savings.
- Raw material costs are also improved; many of the problems associated with color reproducibility have been eliminated entirely.

Table 1: Typical characteristic properties of Aluminum lakes

Average particle size	5–10 µm
Moisture content	12–15%
Oil absorption	40–45 (a)
Specific gravity	1.7–2.0 g/cm^3
pH stability range	4.0–8.0

(a) ASTM D281-31, expressed as grams of oil per 100 g of color. *Source: Hand book of pharmaceutical excipients. pg.no: 507.*

FD&C lakes are available in six basic colors: One yellow, one orange, two reds (a pink-red and an orange-red), two blues (a green-blue and a royal blue)[10].

Blends are available to provide m ore lake colors as needed including brown, green, orange, red, yellow and purple.

Lakes are largely water-insoluble forms of the common synthetic water-soluble dyes. They are prepared by adsorbing sodium or potassium salt of a dye onto a very fine substrate of hydrated alumina, followed by treatment with a further soluble aluminum salt. The lake is then purified and dried[11].
Some examples of Aluminum lakes- Brilliant Blue Lake, Sunset yellow lake, Amaranth lake, Allura red lake, Indigo carmine lake, Quinoline yellow lake.

Inorganic colors or mineral colors

Stability towards light is an important characteristic displayed by this materials, some of which have a useful opacifying capacity, e,g. Titanium dioxide. Another great advantage of inorganic colors is their wide regulatory acceptance, making them most useful for multinational companies wishing to standardize international formulae. On draw back to their use is that the range of colors that can be achieved is rather limited.

Until the discovery of coal tar dyes, mineral pigments were often used to color foods and drugs but because many have toxic effects they were quickly displaced when synthetic dyes became available. Possibly the most important application of, mineral coloring in a present-day medicament is the use of a mixture of red and yellow ferric oxides to give calamine a flesh color. Titanium dioxide is used to color and opacify hard gelatin capsules.

Natural colors or vegetable and animal colors

This is a chemically and physically diverse group of materials. Some of this colors are the products of chemical synthesis rather than extraction from a natural source, for example, β-carotene of commerce I s regularly synthetic in origin. The term frequently applies to such materials is '*nature identical*', which in many ways is more descriptive. Some would even make the case that any product which is not a constituent of the normal diet should not be called 'natural'. This viewpoint would remove colors such as Cochineal and Annatto from consideration. As a generalization, natural colors are not as stable to light as the other group of colors. They do, however, advantage in that they have a wide acceptability. Few medicinally – active vegetable extracts have acceptable colors of their own, especially when diluted in a dispensed preparation, a large number of vegetable coloring matters were used in the past. The only three left in the codex are caramel, formerly called burnt sugar (prepared by heating water-soluble carbohydrates with an accelerator until a black viscid mass is formed), cochineal (a dried insect), and carmine (the aluminum lake of the coloring matter of cochineal). Other examples for natural colorants include Riboflavin and Anthocyanins, Paprika Oleoresin, Beet Root Red, Annatto, Curcumin [Turmeric].

The main disadvantages with the obsolete vegetable colors were- Apart from indigo, a definite chemical compound, most were used as a crude drug or an extract with consequent variation in coloring power and difficulty of standardization. The tinctorial power was very low and often these colors were fugitive in solution. In addition, they are less readily available and more expensive than coal tar colors[12-13].

Physical and chemical properties

Table 2 shows the detailed description about the physicochemical properties of some major colorants.

Table 2: Physical and chemical properties of some certified colorants

FD&C name	Chemical class	Stability to			Tinctorial strength	Hue	Solubility(g/ 100ml) Water	at 25°C 25% Et.OH
		Light	Oxidation	pH change				
Red No. 3 (Erythrosine)	Xanthine	Poor	Fair	Poor	V. good	Bluish pink	9	8
Red No. 40	Monoazo	V. good	Fair	Good	V. good	Yellowish red	22	9.5
Yellow No. 6 (Sunset Yellow FCF)	Monoazo	Moderate	Fair	Good	Good	Reddish	9	10
Yellow No. 5 (Tartrazine)	Pyrazolone	Good	Fair	Good	Good	Lemon Yellow	20	12
Green No. 3 (Fast Green FCF)	TPM*	Fair	Poor	Good	Excellent	Bluish green	20	20
Blue No. 1 (Brilliant Blue FCF)	TPM*	Fair	Poor	Good	Excellent	Greenish Blue	20	20
Blue No. 2 (Indigotine)	Indigoid	V. Poor	Poor	Poor	Poor	Deep blue	1.6	0.5

(TPM * TriPhenyl Methane), *Source: Mendes et* al., *Pharmaceutical Dosage Forms- Tablets, Vol.1, second edition.*

Regulatory status

Coloring agents have an almost unique status as pharmaceutical excipients in that most regulatory agencies of the world hold positive lists of colors that may be used in medicinal products. The legislation also defines purity criteria for the individual coloring agents. In many regions around the world there is a distinction between colors that may be used in drugs and those for food use[14].

- **European union legislation**

The primary legislation that governs coloring matters that may be added to medicinal products is Council Directive 78/25/EEC of 12 December 1977. This Directive links the pharmaceutical requirements with those for foods in the EU. Unfortunately, the Directive makes some specific references to food legislation from 1962 that has subsequently been repealed.

However the European Commission has provided guidance on cross references to the current food color legislation as contained in Council Directive 94/36/EC. In addition, the Scientific Committee on Medicinal Products and Medical Devices has delivered opinions on the suitability and safety of amaranth, erythrosine, canthaxanthin, aluminum, and silver as colors for medicines. Silver was considered unsuitable[15].

- **United states legislation**

The 1960 Color Additive Amendment to the Food Drug and Cosmetic Act defines the responsibility of the Food and Drug Administration in the area of pharmaceutical colorants.

Colors requiring certification are described as FD&C (Food Drug and Cosmetic); D&C (Drug and Cosmetic) or External D&C. The remaining colors are described as uncertified colors and are mainly of natural origin.

➢ **Licensing authority approval**

In addition to national approvals and lists, a pharmaceutical licensing authority can impose additional restrictions at the time of application review. Within the EU this generally takes the form of restricting colors, such as Tartrazine and other azo colors, in medicinal products for chronic administration, and especially in medicines for allergic conditions[16].

The food, drug, and cosmetic act

The Food Drug and Cosmetic Act of 1938 created three categories of coal tar dyes, of which only the first two are applicable to the manufacture of chewable tablets.

- **FD&C colors**: These are colorants that are certifiable for use in foods, drugs, and cosmetics.
- **D&C colors**: These are dyes and pigments considered safe for use in drugs and cosmetics when in contact with mucous membranes or when ingested.
- **External D&C colors**: These colorants, due to their oral toxicity, are not certifiable for use in products intended for ingestion but are considered safe for use in products applied externally[17].

Widely used colorants in pharmaceuticals

➢ **Beta-carotene: (**Beta-carotene; β-carotene; β,β-carotene; E160a**)**

Color Index No**.:** CI 75130 (natural) and CI 40800 (synthetic).

It occurs in the pure state as red crystals when recrystallized from light petroleum. It is capable of producing colors varying from pale yellow to dark orange. It can be used as a color for sugar-coated tablets prepared by the ladle process. However, Beta- carotene is very unstable to light and air, and products containing this material should be securely packaged to minimize degradation. It is particularly unstable when used in spray-coating processes, probably owing to atmospheric oxygen attacking the finely dispersed spray droplets.

Because of its poor water solubility, beta-carotene cannot be used to color clear aqueous systems, and cosolvents such as ethanol must be used. Suppositories have been successfully colored with beta-carotene in approximately 0.1% concentration.

➢ **Indigo Carmine:** (Indigotine; sodium indigotin disulfonate; soluble Indigo blue; E132; FD&C blue #2)

Color Index No**.:** CI 73015

It is a dark blue powder. Aqueous solutions are blue or bluish-purple. The primary use of Indigo carmine is as a pH indicator. Indigo carmine is an indigoid dye used to color oral and topical pharmaceutical preparations and also used with yellow colors to produce green colors.

It is used as a dye in the manufacturing of capsules. Indigo Carmine is also used to color nylon surgical sutures and is used diagnostically as a 0.8% w/v injection.

➢ **Sunset Yellow FCF: (**Yellow orange S., E110; FD&C yellow #6)

Color Index No.: CI 15985

It is a reddish yellow powder. Aqueous solutions are bright orange colored. Sunset yellow FCF is a monoazo dye and is often used in conjunction with E123, Amaranth, in order to produce a brown coloring in both chocolates and caramel. At high concentrations, Sunset Yellow in solution with water undergoes a phase change from anisotropic liquid to a nematic liquid crystal. This occurs between 0.8 M and 0.9 M at room temperature[18].

➢ **Tartrazine:** (Hydrazine yellow; E102; FD&C yellow #5)

Color Index No.: CI 19140

Yellow or Orange yellow powder. Aqueous solutions are yellow-colored. Tartrazine is a monoazo, or pyrazolone, dye. It is used to improve the appearance of a product and to impart a distinctive coloring for identification purposes.

US regulations require that prescription drugs for human use containing Tartrazine bear the warning statement: *This product contains FD&C yellow #5 (Tartrazine)* which may cause allergic-type reactions (including bronchial asthma) in certain susceptible persons. Although the overall incidence of sensitivity to Tartrazine in the general population is low, it is frequently seen in patients who are also hypersensitive to aspirin[19-21].

➢ **Brilliant Blue FCF**: (Erioglaucine; Eriosky blue; Patent Blue AR; E133; Xylene Blue VSG) Color Index No.: CI 42090

It can be combined with Tartrazine (E102) to produce various shades of green. It is widely used in soaps, shampoos, mouth washes[22], and other hygiene and cosmetics applications. It has the capacity for inducing an allergic reaction in individuals with pre-existing moderate asthma[23].

➢ **Titanium Dioxide(TiO2)**: (Anatase titanium dioxide; brookite titanium dioxide; E171; *Kronos 1171*; pigment white 6; rutile titanium dioxide; *Tioxide*; *TiPure*; titanic anhydride; *Tronox*.) Color Index No.: CI 77891

TiO_2 is also an effective opacifier in powder form, where it is employed as a pigment to provide whiteness and opacity to products such as paints, coatings, plastics, papers, inks, foods, medicines (i.e. pills, tablets and also in topical pharmaceutical formulations) as well as most toothpastes[24].

Owing to its high refractive index, titanium dioxide has light-scattering properties that may be exploited in its use as a white pigment and opacifier. The range of light that is scattered can be altered by varying the particle size of the titanium dioxide powder.

It is used as a white pigment in film-coating suspensions, sugar-coated tablets, and gelatin capsules. Titanium dioxide may also be admixed with other pigments.

➢ **Quinoline Yellow SS:** (Solvent Yellow 33; FD&C Yellow #11; Quinoline Yellow A; Yellow No. 204)

Color Index No.: CI 47000

It is a bright yellow dye with green shade. It is insoluble in water, but soluble in non polar organic solvents. Quinoline Yellow SS is used in spirit lacquers, polystyrene, polycarbonates, polyamides, acrylic resins, and to color hydrocarbon solvents. It is also used in externally applied drugs and cosmetics.

➢ **Allura Red AC:** (Allura Red; Food Red 17; E129: FD&C Red 40)

Color Index No.: CI 16035

It has the appearance of a dark red powder. It is approved by the US FDA for use in cosmetics, drugs, and food. This colorant may have slightly less allergy or intolerance reaction by aspirin intolerant people and asthmatics than most of the azo dyes, although those with skin sensitivities should be careful. Allura Red has also been connected with cancer in mice. Not recommended for consumption by children. It is banned in Denmark, Belgium, France, Germany, Switzerland, Sweden, Austria and Norway.

➢ **Quinizarine Green SS:** (Solvent Green 3; Oil Green G; D&C Green #6)

Color Index No.: CI 61565

It is a green dye, an anthraquinone derivative. It has the appearance of a black powder with melting point of 220-221 °C. It is insoluble in

water. It is used for adding greenish coloring to materials. It is used in cosmetics and medications[25].

- **Iron Oxides:**

Iron oxide black (CI 77499); Iron (III) oxide hydrated(CI 77492); Iron oxide red and Iron oxide yellow monohydrate are the various iron oxides used in pharmaceutical preparations.

They occur as yellow, red, black, or brown powder. The color depends on the particle size and shape, and the amount of combined water.

Iron oxides are widely used in cosmetics, foods, and pharmaceutical applications as colorants and UV absorbers. As inorganic colorants they are becoming of increasing importance as a result of the limitations affecting some synthetic organic dyestuffs. However, iron oxides also have restrictions in some countries on the quantities that may be consumed and technically their use is restricted because of their limited color range and their abrasiveness.

Other than the above mentioned colorants, there are many more colorants were under practice; the status of these color additives was described in Table 3.

Table 3: Status of color additives: code of federal regulations (4-1-87)

Color	Used for
FD&C Blue No. 1	May be used for coloring drugs in amounts consistent with cGMP
FD&C Blue No.2	May be used for coloring drugs in amounts consistent with cGMP.
D&C Blue No.4	May be used in externally applied drugs in amounts consistent with cGMP.
D&C Blue No.9	May be used for coloring cotton and silk surgical Sutures including sutures for ophthalmic use in amounts not to exceed 2.5% by weight of the suture.
FD &C Green No. 3	May be used for coloring drugs in amounts consistent with cGMP.
D&C Green No.5	May be used for coloring drugs in amounts consistent with cGMP.
D&C Green NO. 8	May be used in externally applied drugs in amounts not exceeding 0.01% by weight of the finished product.
D&C Orange No.4	May be used for coloring externally applied drugs in amounts consistent with cGMP.
D&C Orange No.5	May be used in mouthwashes and dentifrices and for externally applied drugs in amounts not to exceed 5 mg per daily dose of the drug.
D&C Orange No. 10	May be used for coloring externally applied drugs in amounts consistent with cGMP
D&C Orange No. 11	May be used for coloring externally applied drugs in amounts consistent with cGMP
D&C Orange No. 17	May be used for coloring externally applied drugs in amounts consistent with cGMP
FD&C Red No.3	May be used for coloring ingested drugs in amounts consistent with cGMP.
FD&C Red No. 4	May be used for externally applied drugs in amounts consistent with cGMP.
D&C Red No. 6	May be used for coloring drugs such that the combined total of D&C Red No.6 and 7 does not exceed 5 mg per daily dose of the drug.
D&C Red No.7	May be used for coloring drugs such that the combined total of D&C Red No.6 and 7 does not exceed 5 mg per daily dose of the drug.
D&C Red No.8	May be used for coloring ingested drugs in amounts not exceeding 0.1% by weight of the finished product and for externally applied drugs in amounts consistent with cGMP.
D&C Red No.9	May be used for externally applied drugs in amounts consistent with cGMP.
D&CRedNo.17	May be used for externally applied products in amounts consistent with cGMP.
D&C Red No. 19	May be used for externally applied products in amounts consistent with cGMP.
D&C Red No. 21	May be used for coloring drug product in amounts consistent with cGMP.
D&C Red No. 22	May be used for coloring drug product in amounts consistent with cGMP.

D&C Red No. 27	May be used for coloring drug product in amounts consistent with cGMP.
D&C Red No. 28	May be used for coloring drug product in amounts consistent with cGMP.
D&C Red No. 30	May be used for coloring drug product in amounts consistent with cGMP.
D&C Red No. 31	May be used for externally applied drugs in amounts consistent with cGMP.
D&C Red No. 34	May be used for coloring externally applied in amounts consistent with cGMP
D&C Red No. 39	May be used for external germicidal solutions not to exceed 0.1% by weight of the finished drug product.
FD&C Red No. 40	May be used in coloring drugs Subject to restrictions and in amounts consistent with cGMP
D&C Violet No.2	May be used for coloring externally applied drugs in amounts consistent with cGMP
FD&C Yellow No.5	In general products containing FD&C Yellow No.5 (Tartrazine) must be so labeled. The Code of Federal Regulations should be consulted for use restrictions that may be added.
FD&C Yellow No.6	May be used for coloring drugs in amounts consistent with cGMP.
D&C Yellow No. 7	May be used for externally applied drugs in amounts consistent with cGMP.
D&C Yellow No. 10	May be used for coloring drugs in amounts consistent with cGMP.
D&C Yellow No. 11	May be used for externally applied drugs in amounts consistent with cGMP

Source: *Peck. Baley. McCurdy. and Banker, Pharmaceutical Dosage Forms- Tablets, Vol.1, second edition.*

Coloring systems for various dosage forms

In selecting a colorant for a given application, prime consideration should be given to the type formulation in which the colorant is to be incorporated. Whatever the form of colorant chosen, it should meet as many characteristics as the ideal colorant.

1. Tablets

1.1. Wet granulation

Dissolving water-soluble dyes in a binding solution for the granulating process is the most common approach to coloring a tablet formulating. However, during drying of the granulation, the solution, the soluble colors may migrate and if more than one color is used, the dyes may migrate at different rates. This results in an uneven coloring of the granulation, which will have a mottled appearance after compression. Some additives, such as starches, clays, and talc, have been used to adsorb the dye, there by reducing but not completely eliminating the migration. This entire problem can be avoided by using lakes or other pigments. The colors will not migrate because they are insoluble. In addition, the light stability of the product will be improved.

1.2. Direct compression

Mainly of the economic reason, a growing interest in direct compression formulas has developed. The number of processing steps has been reduced. Direct compression formulation requires blending only; therefore, lakes and other pigments are used because the elimination of the wetting step prevents the effective us of soluble colors.

The dry- coloring of tablets with pigments is not without problems. Although there is little chance of color migration, poor blending of the pigments into the power can result in color specking and "hot spots." This problem can be minimized by pre-blending the pigment with a small part of one of the other ingredients before addition to the entire mixture to reduce pigment particle agglomeration. The ease with which the pigment can be incorporated into the formulation may depend on the components in the mixture.

2. Tablet coating

2.1. Sugar coating

The coloring stage is one of the most critical parts of the operation. It gives the tablet its color and, in some cases, its finished size. Here the success measured in terms of the elegance of the final product. Before the 1950s, traditional color coating for solid dosage forms was usually performed using soluble dyes as the prime colorant. This system can produce the most elegant tablet. However, many difficulties can arise usually related to the dye being soluble.

Color migration readily occurs if the drying stage after each application of color is not handled properly. This results in non-uniform distribution of color or *mottling*. Small depressions or irregularities in the surface of the tablet may also cause non-uniform color. Many smoothing coats are needed before any color can be applied. Care must be taken to ensure that the tablets do not become over colored. Syrups of increasing dye concentrations usually are used to achieve a color match and to control mottling. This operation may take from20 to 60 applications for the color to develop fully. Dye sugar-coating is a very time-consuming and delicate operation.

Late in the 1950s, the pigment sugar-coating process was developed and subsequently patented by *Arnold Nicholson* and *Stanley tucke*[26]. The coloring composition of this invention essentially an aluminum lake and a pacifier dispersed in a syrup solution. This system produced brightly colored, elegant tablets and eliminated many of the problems associated with the standard sugar-coating techniques. The dusty nature of pigments sometimes requires the use of air filtration and dust collection systems to avoid contamination of other areas of the plant.

Today, there are a number of manufacturers who offer color-matched, pre dispersed, pigment sugar-coating concentrates. These concentrates are easily incorporated into the bulk of the syrup-coating solution. The convenience of these concentrates and easily incorporated into the bulk of the syrup-coating solution. The convenience of these concentrates and the ability of the manufacturers to reproduce color batch after batch make these products an attractive alternative to self-preparation of dispersions.

2.2. Film-coating

It resolves many of the problems associated with sugar-coating. It involves the application of a film-forming polymer onto the surface of substrate (such as tablets, granules, and capsules). In addition to the polymer, it also contains plasticizers and colorants, which are needed to achieve the desired properties in the final dosage form. The polymer and the plasticizer are usually dissolved in a solvent to form a coating solution in which the colorants can be dissolved or dispersed. The original film-coating systems used organic solvents for polymer solution.

Today, aqueous systems have largely replaced the organic solvents for environmental reasons. When using organic solvents, water-soluble days can be used as colorants. However, many of the same problems observed in sugar-coating may exist relating to color migration on drying of the films. Additional, because film coatings are relatively thin, small differences in film thickness on tablets may result in significant color variation. There has been some success in using pacified dye systems; however, these systems have been shown to have poorer light stability than pigmented coatings. The colorants of choice of these applications are lakes and inorganic pigments. In addition to providing color, pigments have been reported to reduce moisture diffusion through the film and improve light stability as compared with dye[27].

Commercially available pre-dispersed color mattered pigment concentrates are recommended for use. These concentrates are available both in liquid and in dry forms. The dry forms may contain all of the components needed for a total film-coating system that can be dispersed in water or to her solvents directly at the coating pan.

3. Capsules

3.1. Hard gelatin capsules

The capsules are colored primarily using FD&C or D&C colorants and sometimes an opacifying agent such as Titanium dioxide. The clear type of capsule is colored using water-soluble dyes. Solution of these colors is simply added to the gelatin melt[28].

The pH of the gelatin is important because it can alter the shade of the color. It is also important to control the tackiness of the capsule wall because variations can change color intensity. If the active ingredient is photosensitive, it is advisable to use an opaque capsule. Opaque capsules can contain pigments or dyes and an opacifier. The colorants are usually dissolved or dispersed in water, glycerin or combination of these vehicles before addition to the gelatin mixture. Wall thickness is rarely a factor in determining the shade of an opaque capsule.

Recent technological advances in the area of spin printing have allowed some manufacturers to color identify capsules by printing bands of varying widths and colors on the capsule bodies through the use of colored imprinting inks.

3.2. Soft gelatin capsules or soft gels

Soft Gelatin capsules (soft gels) are one piece, hermetically sealed, soft gelatin shells containing a liquid, a suspension, or a semisolid. Color used in shell has to be darker than color of encapsulating material colors may be natural or synthetic[29].

Opacifier, usually Titanium dioxide, may be added to produce an opaque shell, when the fill formulation is a suspension or to prevent photo degradation of light sensitive fill ingredients. Concentration of opacifier may be up to 0.5%.

4. Liquid products

Dyes should be used that are completely soluble in the particular solvent and at the required concentration. Many times dyes that correspond to the flavor of the product (for example, red for cherry or yellow for lemon) will be chosen. Factors influencing the shade and stability of dyes in the liquid system must be carefully considered as well. These properties are pH, microbiological activity, light exposure in the final product package, and the compatibility of the dye with other ingredients. When formulating liquid products with dyes, the lowest possible concentration of dye needed to give the desired color should be used, because higher concentrations can results in a dull color. Most liquid products have dye concentrations of <0.001%.

If the dye was added directly to the bulk mixing tank, the presence of small amounts of undissolved material would be difficult to determine and could cause additional problems later during the compounding procedure[30].

Pigments or dyes can be used for coloring opaque liquids such as suspensions, emulsions, or imprinting inks. In non-aqueous systems, because of solubility restrictions, the use of pigments is necessary. If pigments are chosen as the colorants, it may be necessary to predispersed them before adding them to the final product. Concentrated dispersions in a wide variety of vehicles are commercially available.

5. Ointments and salves

Both dyes and pigments can be used for coloring ointments and salves, depending on the vehicle. Pigments are preferred because they will not migrate to the surface. To incorporate the pigments into the system, it may be necessary to blend the pigment and the product on a roll or ointment mill[31].

6. Tooth pastes

A major problem impacting the aesthetic appearance of striped toothpaste is the bleeding or migration of color from one component into another. This is especially severe if one colored component is applied to the surface of a white base. For this reason, a colorant that exhibits substantially no visible bleeding is required.

The high density polyethylene entrained colorants of the present invention unexpectedly are substantially non-bleeding when present in conventional toothpaste or gel formations, particularly when contrasted with similar colorants entrained in wax and synthetic polymeric resins including paraffin wax and low density polyethylene. For example, the colorant may be entrained in the High Density Polyethylene" (HDPE) matrix using methods of encapsulation[32].

Blending of colorants

Color combinations can attract or distract. So, while blending the colorants to produce different shades, thorough knowledge about the individual colorant is the prime requirement[33].

The permitted colors do not always give satisfactory shades when used alone but most popular tints and shades can be obtained by blending. For example, Green S gives a greenish blue solution in distilled water and a more satisfactory green is produced by mixing it with Tartrazine as in Green S and Tartrazine Solution B.P.C. Another example, Brilliant Blue FCF can be combined with Tartrazine (E102) to produce various shades of green.

The National Formulary of the United States gives information on the proportion of various water soluble and oil soluble dyes necessary to give particular hues to liquid preparations and drug powders.

Generally Spectral imaging can be used to identify and quantify the colorant in tablets. Combining colorant information with other physical and chemical characteristics can provide a powerful comparison of tablets[34].

Colorants should be protected during processing, use and storage, against

- Oxidizing agents, especially chlorine and hypo chlorites.
- Reducing agents, especially invert sugars, some flavors, metallic ions (especially aluminum, zinc, tin, and iron), and ascorbic acid.
- Microorganisms, especially mold and reducing bacteria.
- Extreme pH levels; especially FD&C Red #3 which is insoluble in acid media and Should not be used below pH 5. O. Also, effects of fading agents such as metals are greatly enhanced by either very high or low pH values.

- The negative activity of reducing and oxidizing agents is greatly enhanced by elevated temperatures.
- Exposure to direct sunlight-FD&C Red #40 and FD&C Yellow #5 have moderate stability to light, while FD&C Blue #2 and FD&C Red #3 have poor light stability. It is important to minimize the exposure of products to direct sunlight, especially products containing dye blends[35].

Concerns still persist about the safety of absorbable dyes despite Completed studies done so far. This has led dye manufacturers and suppliers to develop and test Non-absorbable dyes, which are considered safer by virtue of their non-absorption from the gastrointestinal tract.

Stability and storage conditions

Pharmaceutical coloring agents form a chemically diverse group of materials that have widely varying stability properties[36]. Specific information for selected colors is shown in Table 4.

Table 4: Stability properties of some major colorants

Color	Heat	Light	Acid	Base	Oxidizing agents	Reducing agents
Brilliant blue FCF	Good	Moderate	Very Good	Moderate	Moderate	Poor
Indigo Carmine	Good	Very Poor	Moderate	Poor	Poor	Good
FD&C green 3	Good	Fair	Good	Poor	Poor	Very Poor
Erythrosine	Good	Poor	Insoluble	Good	Fair	Very Poor
Allura red AC	Good	Moderate	Good	Moderate	Fair	Fair
Tartrazine	Good	Good	Good	Moderate	Fair	Fair
Sunset Yellow	Good	Moderate	Good	Moderate	Fair	Fair
D&C yellow #10	Good	Fair	Good	Moderate	Poor	Good

Source: Raymond C Rowe, Paul J, Sheskey and Sian C Owen, Hand book of Pharmaceutical excipients.

While some colors, notably the inorganic pigments, show excellent stability, other coloring agents, such as some organic colors, have poor stability properties but are used in formulations because of their low toxicity[37]. Lakes, inorganic dyes, and synthetic dyes should be stored in well-closed, light-resistant containers at a temperature below 30°C.

For most natural and nature-identical colors, the storage conditions are more stringent and a manufacturer's recommendations for a particular coloring agent should be followed. To extend their shelf-life, some natural colors are supplied as gelatin-encapsulated or similarly encapsulated powders and may be sealed in containers under *Nitrogen*.

To compensate for losses due to fading and other dye loss during processing and storage, some formulators add a slight excess of dye at the beginning. This approach should be cautiously employed since one can obtain unattractive shades when too much color is added at the beginning in an attempt to provide for time-dependent or processing color loss. Regulations covering all aspects of colorants including their procedures for use, provisionally and permanently certified and uncertified color additives, and use levels and restrictions for each coloring additive are covered in the Code of Federal Regulations 21 CFR parts 70 through 82.

Safety

Toxicology studies are routinely conducted on an ongoing basis by organizations such as the World Health Organization (WHO), the US Food and Drug Administration (FDA), and the European Commission (EC). The outcome of this continuous review is that the various regulatory bodies around the world have developed lists of permitted colors that are generally regarded as being free from serious adverse toxicological effects. However, owing to the widespread and relatively large use of colors in food, a number of coloring agents in current use have been associated with adverse effects, although in a relatively small number of people[38-39].

Allura Red AC is not recommended for consumption by children. It is banned in Denmark, Belgium, France, Switzerland, and Sweden[40].

The lake of erythrosine (FD&C red #3), for example, has been delisted in the USA since 1990, following studies in rats that suggested that it was carcinogenic. This delisting was as a result of the Delaney Clause, which restricts the use of any color shown to induce cancer in humans or animals in any amount. However, erythrosine was not regarded as being an immediate hazard to health and products containing it were permitted to be used until supplies were exhausted[41].

Tartrazine (FD&C yellow #5) has also been the subject of controversy over its safety, and restrictions are imposed on its use in some countries; In general, concerns over the safety of coloring agents in pharmaceuticals and foods are associated with reports of hypersensitivity[42-44] and hyperkinetic activity, especially among children[45]. In the USA, specific labeling requirements are in place for prescription drugs that contain Tartrazin as this color was found to be the potential cause of hives in fewer than one in 10 000 people. In the EU, medicinal products containing Tartrazine, Sunset yellow, Carmoisine, Amaranth, Ponceau 4R or brilliant black BN must carry a warning on the label concerning possible allergic reactions. The use of Tartrazine is banned in Norway.

Handling precautions

Pharmaceutical coloring agents form a diverse group of materials and manufacturers' data sheets should be consulted for safety and handling data for specific colors.

In general, inorganic pigments and lakes are of low hazard and standard chemical handling precautions should be observed depending upon the circumstances and quantity of material handled. Special care should be taken to prevent excessive dust generation and inhalation of dust.

The organic dyes, natural colors, and nature-identical colors present a greater hazard and appropriate precautions should accordingly be taken[46].

CONCLUSION

The colorants works as the cosmetics for the pharmaceutical formulations, thus, selection of appropriate colorant for a specific pharmaceutical dosage form plays an important role in manufacturing of the pharmaceutical dosage forms. Since most of the colorants are extremely effective, only minute amounts are necessary to produce the desired color. The Color consistency is important as it allows easy identification of a medication and responsible for the dosage form's aesthetic appearance.

As we can see, selection of colorants for use in global drug development can be very complicated and time consuming. With the differences in colorant regulations worldwide and the need for various performance attributes based on the dosage form, there are numerous considerations that must be assessed. Restrictions or bans on the use of some coloring agents have been imposed in some countries, while the same colors may be permitted for use in a different country. As a result the same color may have a different regulatory status in different territories of the world.

Therefore it is important that appropriate expertise be consulted before finalizing colorant selection to help prevent future development or registration problem.

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