Systemic Review

Helping Ingredients (excipient) in Pharmaceutical formulation: Coloring Agents – use and health concern.

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Introduction

A helping ingredient (excipient) is an inactive substance used as a carrier for the active ingredients of any dosage forms solid, semisolid or liquid. In many cases, an "active" substance (such as Paracetamol) may not be easily administered and absorbed by the living organism; in such cases the substance in question may be dissolved into or mixed with an excipient. Excipients are also sometimes used to bulk up formulations that contain small amount of very potent active ingredients (like Digoxin, Glimepride of Tamsulosin), to allow for convenient and accurate dosage. In addition to their use in the single-dosage quantity, excipients can be used in the manufacturing process to aid in the handling of the active substance concerned. Depending on the route of administration, and dosage form, different excipients may be used. For oral administration tablets and capsules are used, where as Suppositories are used for rectal administration.

To stabilize the active ingredient, excipients are added, ensuring that the active ingredient stays "active", and, just as importantly, stable for a sufficiently up to the time of expiry or the shelf-life of the product that makes it not only competitive with other products but contribute for the treatment of human ailment. Thus, the formulation development with the use of excipients in many cases is considered a trade secret.

Pharmaceutical products often contain agents that have a variety of purposes, including improvement of the appearance, bioavailability, stability, and palatability of the product. Excipients (substances added to confer a suitable consistency or form to a drug, such as the vehicle, preservatives, or stabilizers) frequently make up the majority of the mass or volume of oral and parenteral drug products. These pharmaceutical adjutants are usually considered to be inert and do not add to or affect the intended action of the therapeutically active ingredients.

US Food and Drug Administration (FDA) approved 773 chemical agents for use as inactive ingredients in drug products. Inasmuch as these compounds are classified as "inactive," no regulatory statutes require listing on product labeling. Pharmacopeial guidelines, enforceable under the legal provisions, do require labeling of inactive ingredients for topical, ophthalmic, and parenteral preparations; orally administered products are currently exempt. Strong consumer pressure around the globe is asking complete disclosure of all ingredients, voluntary labeling was adopted by the two major pharmaceutical industry trade associations. These voluntary guidelines contain an exemption for "trade secret" components and do not require complete disclosure of all fragrance and flavoring ingredients.

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Current problems encountered with "inactive" ingredients include benzalkonium chloride-induced bronchospasm from antiasthmatic drugs, aspartame (an artificial sweetener) induced headache and seizures, saccharin (another artificial sweetener)induced cross-sensitivity reactions in children with sulfonamide allergy, benzyl alcohol toxicity in neonates receiving high-dose continuous infusion with preserved medications, dye-related cross-reactions in children with aspirin intolerance, lactose(a common excipent of capsule and tablet dosage form) induced diarrhea, and propylene glycol (a non-aqueous vehicle) induced

hyperosmolality and lactic acidosis. Although many other excipients have been implicated in causing adverse reactions, these are the most significant in the pediatric patients. Omission and inaccuracy of drug labeling information on pharmaceutical excipients may expose susceptible individuals to adverse reactions caused by preservatives and dyes. Complications of inadvertent intake of sugar-containing medicines by diabetics, or aspartame intake by patients with phenylketonuria may also occur.

In the pharmaceutical formulation excipients may be: preservatives, dyes, flavorings, sweeteners, thickeners, emulsifiers, stabilizers or antioxidants. They keep medication free from micro-organisms and proper for consumption for longer time spans, besides making them tasty and thus favoring treatment compliance. Most excipients are used in low concentrations, thus adverse reactions are rare1. However, they may trigger undesirable effects due to intolerance - a non-immune mechanism which leads to anaphylactic reactions and idiosyncrasies - or allergies - immune mechanism which may result in immediate or late hypersensitivity4. In clinical practice these reactions are commonly and mistakenly attributed to the medication active principle.

The earliest pill emerged in ancient Egypt as a little round ball containing medicinal ingredients mixed with clay or bread. For the next five thousand years - up until the middle of the 20th century - pills were round and white. Color was almost non-existent. “Over the counter” medications were only available as tablets in ghostly white or pasty pastel hues; likewise prescription medications were colorless pills encased in clear or transparent orange vials. Liquids, with the exception of Pepto-Bismol’s pink, were drab as well.

History of Colors in Food

History of Colors in Food There is ample evidence that early civilizations introduced color into their food. Ancient Egyptians colored food yellow with saffron and saffron is mentioned in Homer's Iliad, dating from 700 B.C.E. Pliny the Elder relates that wines were artificially colored in 400 B.C.E. Wealthy Romans ate white bread that had been whitened by adding alum to the flour.

In the great houses of medieval Europe, cooks employed plant extracts of many hues. Along with the period's painting and stained glass, the cuisine of the late Gothic period was informed by rich and ornate color. Parti-colored dishes, jewel-toned cordials, and shimmering jellies were colored red, purple, blue, green, and yellow. Saffron had migrated from Persia as far as England by the mid-fourteenth century, and indigo, turnsole, alkanet (borage root), red saunders (a powdered wood), marigold, turmeric, safflower, parsley, spinach, fruits, and flower petal extracts commonly colored the foods of the wealthy.

In the early Renaissance (1470–1530), a common belief in Europe, based on Arabic ideas, was that color in food not only indicated nutritional value, but also inherent medicinal power connected to spiritual, celestial substances. Eating sweet red grapes produced full rich blood, black food like pepper or fungi induced melancholy, and coloring foods golden promoted divine solar healing. The British chemist Sir William Henry Perkin created the first synthetic dye, mauveine, in 1856 by oxidizing aniline. By the end of the century, eighty synthetic dyes colored foods, and coal tar derivatives were the principle source of synthesized dyes. Americans and Europeans were consuming varieties of unregulated, artificially colored food, including jellies, butter, cheese, ice cream, sausage, pasta, and wine.

Government and consumers' concerns regarding food additives intensified in the 1950s with new scientific findings. In 1960 the U.S. Congress passed the Color Additives Amendment to the FD&C Act, which placed the burden of establishing safety on the food manufacturing industry and created a new category, "color additives exempt from certification." This

includes both "natural colors" and "nature-identical" colors (those synthetically made but chemically identical to natural colors, like beta-carotene and canthaxanthin). Since the 1970s the inclusion of colorants in food has received considerable scrutiny based primarily on concerns regarding the carcinogenic properties of colorants. In 1992 a U.S. court decision interpreted the Delaney Clause to mean that zero levels of carcinogens are permissible. With further research findings, certified colors continue to be delisted.

Food Coloring Regulation

Government attempts to regulate coloring agents in food have had a long history. There was a 1396 edict in Paris against colored butter. In 1574 French authorities in Bourges prohibited the use of color to simulate eggs in pastries, and Amsterdam forbade annatto for coloring butter in 1641. Denmark listed colors permitted for food coloring in 1836, and Germany's Color Act of 1887 prohibited harmful colors in food. A report to the British Medical Association in Toronto in 1884 resulted in the Adulteration Act, the first list of prohibited food additives. Australia passed the Pure Food Act in 1905.The United States Food and Drug Act of 1906 restricted synthetic food colors to those that could be tested as safe. Of the eighty colors in use, only seven were approved as certified colors. In 1938 the Food, Drug, and Cosmetics (FD&C) Act approved fifteen dyes for use in food, drugs, and cosmetics and assigned color numbers instead of their common names (thus, amaranth became Red No. 2).

Colors in Pharmaceutical dosage forms

The color transformation started in the '60s and accelerated in mid seventies of last century, when the new technology of “soft gel” capsules made colorful medications possible for the first time. Shiny primary colors such as cherry red, lime green and tangy yellow arrived first. Today's gel caps can be tinted to any of 80,000 color combinations. As for tablets, continuous advancements in technology consistently bring new and colorful coating products to market.

The earliest pill emerged in ancient Egypt as a little round ball containing medicinal ingredients mixed with clay or bread. For the next five thousand years - up until the middle of the 20th century - pills were round and white. Color was almost non-existent. “It is claimed that Patients respond best when color corresponds with the intended results of the medication. For example, calm blue for a good night's sleep and dynamic red for speedy relief. Or consider a reverse scenario: fire red capsules for acid reflux or murky bile green for nausea.

A similar benefit is rooted in the synaesthetic effects of color - and specifically a color's associations with smell and taste. Although technically we don't “eat” pills, we do taste and swallow them. What would a grey tablet taste and smell like? Smoky, fruity or moldy? How about a pink pill? Sour, bitter, or sweet? Which one would be easier to swallow? Furthermore, synaesthetic effects of colors also include associations with temperature. For example, a blue pill is cool, an orange pill, hot. Numerous dyes are used in pharmaceutical manufacturing. These dyes give products a distinctive, identifiable appearance, and they impart a uniform and attractive color to products that might otherwise be drab and unappealing or exhibit color variation among batches.

Aside from countless functional benefits for the consumer, color is now playing an even more powerful role in transforming the plain white pill into a unique, brand image. This has become even more significant due two recent events that have transformed marketing – and the role of color - in the pharmaceutical industry.

Customers are shopping for medications in the departmental stores. In fact, today in the developed world 73% of Over the Counter (OTC) medicines are purchased now from the departmental stores. Therefore, it's even more important for pharmaceutical products to catch

consumer's eye being attractive. It is impossible t\o achieve without the help of colors and colorful presentation. So as the competition heats up, color and design are critical to the brand. Consider the packaging and advertising for the new OTC medicines. Health workers are also looking for attractive and fancy packaging that forced for development of the packaging industry.

We are more concern about the colorful pharmaceutical dosage form. In Nepal people do not percept those cough syrups other than red color (cherry red color of Amaranth) and vitamin other than yellow color (of riboflavin). Moreover Color consistency is important as it allows easy identification of a medication.

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Consequently, drug companies are leaving nothing to chance. The color and shape of the dosage forms, and the names and imagery used to sell products are heavily researched and tested, in the developed world much like the drugs themselves.

Color has been elevated to a “powerhouse” status because it is the most fundamental part of a drug's personality. As is the case with all products – from computers to colas - purchasing decisions are not just based on what a product looks like (visual brand) but on the idea of the brand (its core brand value), how customers feel about it (emotional brand). In other words, color has the unique ability to do all three simultaneously – to create emotional appeal, to communicate functional values and benefits (such as reliable pain relief), and to distinguish the brand from others.

On the other hand, color may not matter in the future of prescription medications tablets and capsules. Scientists have created a coin-sized microchip drug dispenser that may be implanted under the skin. It would be programmed to release medications in concentrated formulas -- all on different schedules. Sensors may even be attached to the chip to detect the level of a drug in your body and then add more as needed.

Measuring the color of pharmaceutical products can be a challenge. They are in many forms including powders, solids (tablets, caplets, capsules, gels), creams, as well as syrups and other liquids. They can be opaque, translucent and transparent. There may only be a small amount to measure or the sample may be small in physical size.

In the pharmaceutical industry color (or lack of color) is used as:

- An indicator of quality
- To differentiate between medications
- To indicate test results on dip strips
- Part of a brand's identity
- An indicator of degradation and loss of potency over time

Certified FD&C Colors can generally be used in Foods, Drugs, and Cosmetics and D&C Colors can be used in Drugs and Cosmetic, but not in foods.

A **dye** is a distinct chemical that exhibits coloring power when it is dissolved. Dyes are water soluble, and will not mix with oils. Dyes can be purchased in a Powder format or a less dusty version called "Granular".

An **aluminum lake pigment** is an insoluble material that tints by dispersion. Lakes are produced from the FD&C Dyes and are oil dispersible (but generally not oil soluble) and thus can be mixed with oils and fats. They can also be dispersed in other carriers such as propylene glycol, glycerin and sucrose (water and sugar).

Lakes are made by combining dyes with salts to make insoluble compounds. Lakes tint by dispersion. Lakes are not oil soluble, but are oil dispersible. Lakes are more stable than dyes and are ideal for coloring products containing fats and oils or items lacking sufficient moisture to dissolve dyes.

Natural food dyes

A growing number of natural food dyes are being commercially produced, partly due to consumer concerns surrounding synthetic dyes. Some examples include: Caramel, made from caramelized sugar, used in cola products and also in cosmetics, Annatto , a reddish-orange dye made from the seed of the achiote. A green dye made from chlorella algae (chlorophyll), Cochineal, a red dye derived from the cochineal insect, Dactylopius coccus, Betanin extracted from beets Turmeric (curcuminoids), Saffron (carotenoids), Paprika Elderberry juice, Pandan (Pandanus amaryllifolius), a green food coloring and Butterfly pea (Clitoria ternatea), a blue food dye. To ensure reproducibility, the colored components of these substances are often provided in highly purified form, and for increased stability and convenience, they can be formulated in suitable carrier materials (solid and liquids. Hexane, acetone and other solvents break down cell walls in the fruit and vegetables and allow for maximum extraction of the coloring. Residues of these often remain in the finished product, but they do not need to be declared on the product. This is because they are part of a group of substances known as carry-over ingredients.

Artificial colors dyes

Artificial colors are FD&C Blue No. 1 – Brilliant Blue FCF, E133 (blue shade), FD&C Blue No. 2 – Indigotine, E132 (dark blue shade), FD&C Green No. 3 – Fast Green FCF, E143 (turquoise shade), FD&C Red No. 40 – Allura Red AC, E129 (red shade), FD&C Red No. 3 – Erythrosine, E127 (pink shade, commonly used in glacé cherries), FD&C Yellow No. 5 – Tartrazine, E102 (yellow shade) and FD&C Yellow No. 6 – Sunset Yellow FCF, E110 (orange shade). The above seven artificial colors are known as "primary colors"; when they are mixed to produce other colors, those colors are then known as "secondary colors".

Colors and health concern

Norway banned all products containing coal tar and coal tar derivatives in 1978. New legislation lifted this ban in 2001 after EU regulations. As such, many FD&C approved colorings have been banned; Tartrazine causes hives in less than 0.01% of those exposed to it. Erythrosine is linked to thyroid tumors in rats. Cochineal, also known as carmine, is derived from insects and therefore is neither vegan nor vegetarian. It has also been known to cause severe, even life-threatening, allergic reactions in rare cases. FD & C Yellow No. 5 contains tartrazine. People who have aspirin sensitivity may not tolerate it and it may be especially a bad choice for people who have frequent asthma. Tartrazine is derived from coal tar, which has led to concerns for all people who consume it. FD & C Red No. 3 contains

erythrosine, another coal tar based compound. There is suspicion that this colorant may be carcinogenic. Rat studies showed development of thyroid tumors when high doses of erythrosine were administered.

Several groups of dyes have been associated with serious adverse effects. The azo dye tartrazine (FD&C Yellow No. 5) is known to be potentially dangerous in aspirin-intolerant individuals. Approximately 2% to 20% of asthmatics are sensitive to aspirin. The incidence of cross-reaction to tartrazine was previously believed to be as high as 10%.Unlike aspirin; tartrazine does not alter prostaglandin synthesis and does not, therefore, exert anti-inflammatory actions. Nonetheless, reactions to tartrazine are similar to those produced by aspirin, occur in patients both with and without a history of aspirin intolerance, and include acute bronchospasm, nonimmunologic urticaria, eosinophilia, and angioedema. Patients with recurrent allergic vascular purpura may experience exacerbations after exposure to azo dyes, such as tartrazine and sunset yellow. Because of both the seriousness of these reactions and the widespread use of tartrazine in foods and over-the-counter and prescription drugs. Anaphylactic reactions may also develop similar reactions from dyes other than tartrazine, including amaranth, erythrosine, indigo carmine (FD&C Blue No. 2), ponceau, sunset yellow, Brilliant Blue (FD&C Blue No. 1), methyl blue,120 quinolone yellow, and FD&C Red No. 40.

Gastrointestinal intolerance, with abdominal pain, vomiting, and indigestion, has been associated with sunset yellow; in one case, eosinophilia and hives were also present. Other dermatologic reactions, including photosensitivity, erythroderma, and desquamation have been attributed to erythrosine, an iodine-containing dye. By mandate, erythrosine has been removed from topical products and is being voluntarily removed from many oral drug products because of concerns about carcinogenicity.

Contact dermatitis has been associated with neutral red, D&C Yellow No. 11, indigo carmine (FD&C Blue No. 2), quinoline yellow, and gentian violet (CI Basic Violet No. 3).

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