European Journal of Pharmaceutical Sciences 93 (2016) 264–273

Contents lists available at ScienceDirect

European Journal of Pharmaceutical Sciences

journal homepage: www.elsevier.com/locate/ejps

Review

Safety and regulatory review of dyes commonly used as excipients in pharmaceutical and nutraceutical applications

Leire Pérez-Ibarbia [a], Tobias Majdanski [b,c], Stephanie Schubert [c,d], Norbert Windhab [a], Ulrich S. Schubert [b,c,*]

[a] Evonik Nutrition & Care GmbH, Kirschenallee, 64293 Darmstadt, Germany
[b] Laboratory of Organic and Macromolecular Chemistry (IOMC), Friedrich Schiller University Jena, Humboldtstrasse 10, 07743 Jena, Germany
[c] Jena Center for Soft Matter (JCSM), Friedrich Schiller University Jena, Philosophenweg 7, 07743 Jena, Germany
[d] Institute of Pharmacy, Friedrich Schiller University Jena, Otto-Schott-Straße 41, 07743 Jena, Germany

ARTICLE INFO

Article history:
Received 19 May 2016
Received in revised form 20 July 2016
Accepted 11 August 2016
Available online 12 August 2016

Keywords:
Dye
Excipients
Coloring agents
Safety
Regulation
Toxicology
Pharmaceutical
Nutraceutical

ABSTRACT

Color selection is one of the key elements of building a strong brand development and product identity in the pharmaceutical industry, besides to prevent counterfeiting. Moreover, colored pharmaceutical dosage forms may increase patient compliance and therapy enhancement. Although most synthetic dyes are classified as safe, their regulations are stricter than other classes of excipients. Safety concerns have increased during the last years but the efforts to change to natural dyes seem to be not promising. Their instability problems and the development of "non-toxic" dyes is still a challenge. This review focuses specifically on the issues related to dye selection and summarizes the current regulatory status. A deep awareness of toxicological data based on the public domain, making sure the compliance of standards for regulation and safety for successful product development is provided. In addition, synthetic strategies are provided to covalently bind dyes on polymers to possibly overcome toxicity issues.

Contents

* Corresponding author at: Evonik Nutrition & Care GmbH, Kirschenallee, 64293 Darmstadt, Germany.
E-mail address: ulrich.schubert@uni-jena.de (U.S. Schubert).

http://dx.doi.org/10.1016/j.ejps.2016.08.026
0928-0987/

1. Introduction

According to Abrahart, a dye possesses color because it absorbs light in the visible spectrum (400 to 700 nm), has at least one chromophore (color bearing group), has a conjugated system (structure with single and double bonds) and exhibits resonance of electrons (Abrahart, 1977). If one of these characteristics is missing, the color is typically lost. This technical pragmatic definition does not exclude future developments for modern quantum matters or material based on interference physics performed on insect phenotypes. Historically, colorful appearance was interpreted as a sign of intended or desired pharmaceutical effects and led to screening discoveries. Until the middle of the nineteenth century, the coloring agents used in cosmetics, drugs and food were obtained from animals, plants and minerals. However, the discovery in 1856 of Mauveine as the first synthetic dye by William Perkin boosted the chemical industry, and synthetic dyes became principal constituents for food and drugs (Hunger, 2003). As an example, the fascination of P. Ehrlich on synthetic dyes with ability to stain and target microorganisms led him to discover Salvarsan®, an arsenic-aniline compound, which was used for the treatment of syphilis. Basing on it, the dye could be included in a molecule, which is toxic for the microorganism, and behaves as chemotherapeutic agent (Lloyd et al., 2005).

For a number of years, there have been increasing concerns regarding the safety of synthetic dyes, and the issue whether natural dyes could replace synthetic dyes has been requested. Innumerous efforts have been made to extract dyes from colored plants and flowers but those attempts failed because most natural dyes are not very stable (Cristea and Vilarem, 2006). Furthermore, dyes have been strictly subjected to toxicity standards, and, as result, a number of colorants have been removed from the list of Food, Drug and Cosmetic Act (FD&C) (Barrows et al., 2003).

The dyes available do not meet all the criteria required for the ideal pharmaceutical colorant. The acceptable daily intake (ADI), toxicological data and slight difference in international regulations are the three key aspects determining color amount and type permitted. Previous reviews concluded the importance of the following regulatory aspects of dyes offering little information about data regarding toxicology (Kanekar and Khale, 2014). On the other hand, dye companies rarely provide information about the compliance to the regulations and toxicological data. Hence, the formulator has to access to data already in the public domain in order to be updated and have technical understanding for selecting an adequate color according to his need.

However, the current research demonstrates that there is a clear evidence that dyes affect the behavior of children including those with food allergies, hyperactivity, Attention-Deficit/Hyperactivity Disorder (ADHD) and without any allergic or behavior disorder (Lefferts, 2016). A controversial example, Ritalin®, used for the treatment of children with ADHD, contains the two food dyes quinoline yellow (D&C Yellow No. 10) and fast green FCF (FD&C Green No. 3), which may exacerbate the disorder and shows that the need of a formulation containing safe dyes is of high priority. In addition, there have been a number of updates of the toxicological data of dyes, many of which related to the European Food Standards Authority (EFSA) opinions. Consequently, some of the safety threshold values have been lowered.

Therefore, this review is intended to provide, even though a palette of dyes are available worldwide with regulations, a deep awareness of toxicological data based on EFSA opinions, allowing the formulator to decide himself, which dye is suitable for each formulation and making sure the compliance of standards for regulation and safety. Furthermore, the review provides future aspects and new horizons regarding the safety of dyes for this purpose. Therefore, it is summarized that polymers with covalent bonded food dyes show improved characteristics correlating to the mentioned problems. The increase of the molar mass inhibits the adsorption by the gastro intrinsic system, which lowers or eliminates toxic effects (Dawson and Rudinger, 1975; Honohan et al., 1977; Konstantinova et al., 1999; Wang and Wingard, 1982). There are several routes to synthesize polymers bearing covalently bound food dyes (Dawson et al., 1976; Dawson et al., 1981; Dawson and Rudinger, 1975; Kaastrup and Sikes, 2015; Konstantinova and Bojinov, 1998). One recent example are novel polymeric-dyes, which can be applied as coating excipients for pharmaceuticals and nutraceuticals and demonstrate the safety of these polymers bearing covalently bound dyes (Pérez-Ibarbia et al., 2016). However, the number of successful and applicable examples is rather limited.

2. Dye classification

Dyes may be classified according to their chemical structure or by use or by application method. This classification then would allow at least in principle for a structure-safety consideration including its simplifying and, thus, misleading generalizations. In the chemical classification, dyes are grouped according to certain common chemical structural features (chromophores) whereas the classification by application or usage is the principal system adopted by the Color Index (C.I.) (Society of dyers and colorists, 1971). Based on this classification, only dyes that are used for food, drugs and cosmetics will be mentioned in this review. They belong to azo, carotenoid, indigoid, quinophtalone, triarylmethane and xanthene chemical types (Hunger, 2003). The structures of the functional groups are shown in Fig. 1. Azo dyes are synthetic compounds that contain two aromatic rings connected by a N=N double bond. They are the largest group of dyes including Amaranth, Sunset Yellow FCF and Tartrazine among others (Hunger, 2003). Carotenoid dyes can be natural or synthetic compounds containing long systems of double and single bonds (Bechtold and Mussak, 2009). Indigoid dyes are based on indigo. Indigo Carmine is the most commonly used dye for pharmaceutical application. Most of them are synthetic but indigo itself occurs in nature. Quinophtalone dyes are based on naphthalene-quinone structure. Quinoline Yellow is the most used one, which consists of a mixture of mono- and disulfonate salts (Hunger, 2003; Podczeck and Jones, 2004). Triarylmethane dyes are synthetic organic compounds containing triphenylmethane backbones (Smith and Hong-Shum, 2011). Brilliant Blue FCF and Patent Blue are the most used in the pharmaceutical industry. Xanthene dyes are chemically based on a xanthene nucleus. Erythrosine is well-known for oral pharmaceutical dosage forms (Podczeck and Jones, 2004).

3. Rationale for coloring of pharmaceuticals and nutraceuticals with dyes

Coloring agents or colorants are excipients used in the pharmaceutical industry to impart color to pharmaceutical dosage forms (Abrahart, 1977). Coloring agents can be either dyes or pigments. The difference between them is solubility. Natural and organic dyes are soluble in the medium in which they are applied, whereas pigments are insoluble, staying suspended in a liquid (Zollinger, 2003). Numerous coloring agents are used in pharmaceutical manufacturing to provide products a distinctive, identifiable appearance and to impart a uniform and attractive color. For example, many commercial medicaments do not differ optically and may confuse the patients leading to medical errors. Therefore, the more different is the size, shape and color of