ANALYSIS OF SYNTHETIC DYE USE (TRIPHENYLMETHANE, QUINOLINE, XANTHENE CLASSES) IN PHARMACY AND THEIR TOXICOLOGICAL IMPLICATIONS

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RESEARCH ARTICLE

Abstract

The use of food dyes in both the food and pharmaceutical industries can be beneficial for appearance, identification, and masking unpleasant tastes. However, this practice must be done responsibly, by adhering to regulations and prioritizing consumer safety.

In this paper, we identified the most frequently used dyes from the triphenylmethane, quinoline, and xanthene classes employed as excipients in the preparation of various pharmaceutical dosage forms. To achieve this, we analyzed 50 pharmaceutical products sold in an open-circuit pharmacy in Bihor County.

Keywords: dyes, triphenylmethane, quinolein, xanthenic class
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INTRODUCTION

In the food industry, synthetic dyes are used to replace the natural color of the food product, which is often lost during processing. This is done despite studies demonstrating that the color provided by the dye can alter biochemical laboratory analyses and the histopathological structure of the liver and kidneys if food products containing them are consumed (Soltan & Shehata, 2012).

In the pharmaceutical industry, dyes are used as excipients in various dosage forms that are intended to be colored, such as tablets, capsules (hard and soft gelatin capsules), oral solutions, ointments, etc. The purpose of using these dyes is to improve the aesthetic appearance and to increase the preparation's stability (Biswal et al., 2015). Dyes are added to foods, supplements, and medicines for commercial, psychological, or practical reasons (Šuleková et al., 2016).

In the cosmetic industry, dyes are used, either alone or in combination, in proportions ranging from 1–25% to color products such as lipsticks, blushes (or eye shadows), mascaras, eyeliners (or eye pencils), nail polishes, and hair dyes (Ardila-Leal et al., 2021).

With the development of industry, especially the food and pharmaceutical sectors, several classes of dyes emerged and their use significantly increased. Alongside this expanded usage across various economic branches, the risk of toxic effects also grew considerably. In the 1980s, a study was conducted which revealed that approximately 280,000 tons of textile dyes are discharged annually worldwide into industrial effluents.

The path of these discharged dyes into the environment is concerning: after reaching surface water, they infiltrate the groundwater, posing a risk to consumers and the entire ecosystem. It has been demonstrated that once in the water, they can be a risk factor because these dyes cannot be broken down by the standard treatments applied to wastewater, raw water, or industrial effluents. This difficulty in

degradation is primarily due to their very complex chemical structures.

Another risk factor for human health is skin exposure to dyes, either in the workplace or through the use of various cosmetic products. When absorbed through the skin, these dyes can potentially lead to mutagenic, cytotoxic, and genotoxic effects (Scientific Committee on Cosmetic Products and Non-food Products intended for Consumers, 2002).

The absorption of dyes through the skin has been demonstrated *in vitro* using both mouse and human skin, both of which were shown to be capable of reductively cleaving the dye (Sandu, 2014). This reductive process occurs in the presence of enzymes found in gastric juices, saliva, or sweat.

It has been proven that these dyes are responsible for mutagenic or carcinogenic effects, effects which are actually caused not by the dyes themselves, but by their breakdown products. This finding has led to the prohibition of these dyes for food use in several countries (Neniţescu, 2015). Other potential side effects of dyes include the development of allergies; their decomposition can release histamine, which may intensify asthma; and they can lead to hyperactivity and reduced concentration in children.

The objective of the study is to identify the most commonly used dyes from the triphenylmethane, quinoline, and xanthene classes employed as excipients in the preparation of various pharmaceutical dosage forms.

The triphenylmethane group includes Patent Blue V (E131, the dicalcium salt of m-hydroxytetraethyl-diamino-triphenyl-carbinol-disulfonic acid anhydride) and Brilliant Green (E133, the disodium salt of 4[4-(N-ethyl-p-sulfobenzylamino)-phenyl]-(2 sulfonium phenyl)-methylene-[1-(N-ethyl-N-p-sulfobenzyl)-2,5 cyclohexadiene-imine), both of which produce green or blue colors (see Figure 1) (Necula & Babii, 2010).

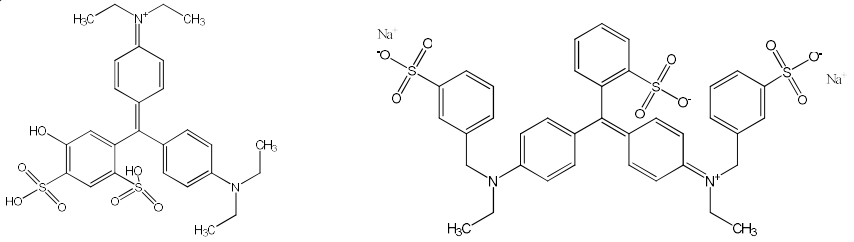

Figure 1. **Chemical structures of patent blue V (E131) and brilliant blue FCF (E133)**

From the xanthene class of dyes, the only one authorized for use as a food additive is Erythrosine (E127, the dipotassium or disodium salt of tetra-2′, 4′, 5′, 7′ tetraiodofluorescein).

The dye from the quinoline group used as an additive is Quinoline Yellow (E104, the disodium salt of 2-quinolyl-2-indandione-1,3-disulfonic acid), (see Figure 2)(Necula & Babii, 2010).

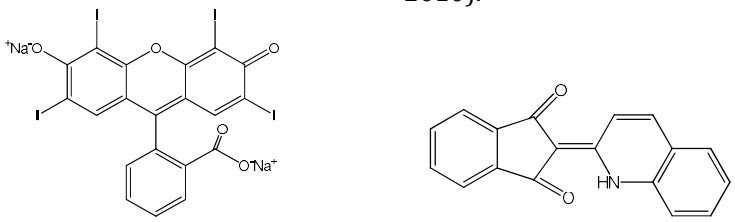

Figure 2. **Chemical structures of erythrosine (E127) and quinolein yellow (E104)**

MATERIAL AND METHOD

The study conducted involves the analysis of dye content—specifically those from the triphenylmethane, quinoline, and xanthene classes—in various pharmaceutical products sold in an open-circuit pharmacy in Bihor County.

The products analyzed include:

- RX (prescription-only medicines)
- OTCs (over-the-counter medicines)
- Dietary Supplements (DS).

The pharmaceutical products analyzed are presented in Table 1.

Table 1.

Pharmaceutical products analyzed, pharmaceutical form, type of dye used, and manufacturing country

Notation	Pharmaceutical form	Type of dye used (E)	Manufacturing Country
RX1	Capsules	104, 110, 122, 171	Romania
RX2	Capsules	104, 110, 124, 133, 171	Romania
RX3	Capsules	104, 110, 124, 133, 171	Romania
RX4	Capsules	104, 132, 171	Slovenia
RX5	Capsules	104, 132, 171	Slovenia
RX6	Capsules	104, 132, 133, 171	Romania
RX7	Capsules	131,171, 172	Romania
RX8	Extended-release capsules	102, 110, 129, 133, 171	Slovenia
RX9	Extended-release capsules	110, 124, 133, 171	Slovenia
RX10	Extended-release capsules	102, 110, 129, 133, 171	Slovenia
RX11	Extended-release capsules	10, 129, 133, 171	Slovenia
RX12	Extended-release capsules	110, 127, 129, 133, 171	Slovenia
RX13	Tablets	110, 1292, 133	Poland
RX14	Tablets	133	Poland
RX15	Tablets	120, 133	Poland
RX16	Dragees	104, 171	Austria
RX17	Capsules	104, 127, 133, 142, 171	Romania
RX18	Capsules	110, 124, 133, 151, 171	Romania
OTC1	Pills	104, 110, 122, 171	Romania
OTC2	Tablets	104	Poland
OTC3	Tablets	104, 110, 122	Czech Republic
OTC4	Pills	104	Great Britain
OTC5	Pills	104	Great Britain
OTC6	Gelatin capsules	104, 110, 218	Germany
OTC7	Capsules	104, 110, 171, 216, 218	Romania
OTC8	Pills	104, 132, 951, 953	Italy
OTC9	Capsules	127, 171, 172	Romania
OTC10	Capsules	127, 171	France
OTC11	Film-coated tablets	127	Czech Republic
OTC12	Capsules	127, 132, 171	France
OTC13	Film-coated tablets	127, 171	Czech Republic
OTC14	Film-coated tablets	127, 171	Czech Republic
OTC15	Sachets	104, 110	Germany
OTC16	Capsules	104, 320, 951	Germany
OTC17	Sachets	104, 110	Germany
OTC18	Film-coated tablets	127, 171	Romania
OTC19	Capsules	104, 122, 133, 171	Romania
OTC20	Sachets	104	Spain
OTC21	Film-coated tablets	104, 110, 171	Ireland
OTC22	Sachets	104, 32 , 951	Great Britain
OTC23	Gelatin capsules	104, 131, 171, 420	Italy
OTC24	Capsules	104, 132	Czech Republic
OTC25	Capsules	104, 127, 133, 142, 171, 216, 218	Romania
OTC26	Gelatin capsules	102, 131	Romania
OTC27	Gelatin capsules	131	Romania
OTC28	Gelatin capsules	131, 171	France
OTC29	Pills	133	Slovenia
OTC30	Effervescent tablets	104, 127, 420	Ireland
OTC31	Pills	133, 953	Slovenia
SA1	Capsules	104, 127, 133	Romania

The products included in the study were analyzed based on several criteria: the classification of their pharmaceutical form, the country in which they were manufactured, the number of dyes they contain from the triphenylmethane, quinoline, and xanthene classes, the number of E-numbers used in the formulation of the analyzed products from the manufacturing country, the pharmaceutical forms in which the dyes are most frequently used, and the dye class that is most commonly utilized.

RESULTS AND DISCUSSIONS

Out of the total of 50 pharmaceutical products included in the study, the analysis

covered 18 prescription-only medicines (RX), 31 over-the-counter medicines (OTCs), and 1 dietary supplement (see Figure 3).

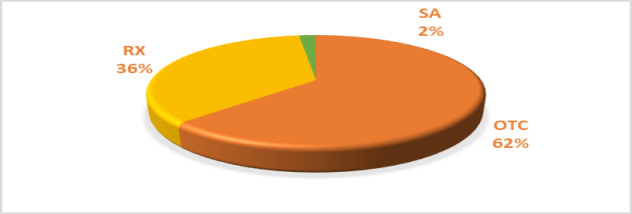

Figure 3. **Number of RX, OTC and supplements from which dyes were analyzed**

By analyzing the products included in the study, it is observed that the majority are Over-The-Counter medicines (OTCs), representing 62% of the sample, which are available in pharmacies without a medical prescription. Next are the Prescription-Only medicines (RXs) at 34%, which require a medical prescription, followed by only a single dietary supplement.

The pharmaceutical products analyzed were manufactured by various pharmaceutical companies, both domestic and foreign (see Figure 4). The breakdown by country is as follows: Romania (16), Poland (4), Czech Republic (5), Great Britain (3), Germany (4), Slovenia (9), Italy (2), France (3), Spain (1), Ireland (2), and Austria (1).

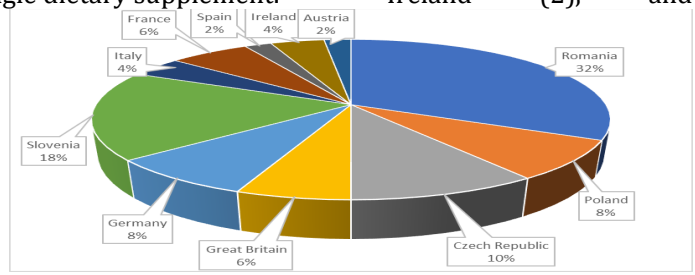

Figure 4. **Breakdown of the products taken in the study by the country in which they were produced**

Following the study, we observed that 32% of the analyzed products were manufactured in Romania, 18% in Slovenia, 10% in the Czech Republic, 8% in Poland and Germany, 6% in France and Great Britain, 4% in Italy and Ireland, and 2% in Spain and Austria.

Based on the study of the products, categorized by the total number of E-numbers they contain, we observed the following (see Figure 5): 26% contain 3 E-numbers, 22% contain 2 E-numbers, 16% contain 1, 4, or 5 E-numbers, and 2% contain 6 or 7 E-numbers (see Figure 5).

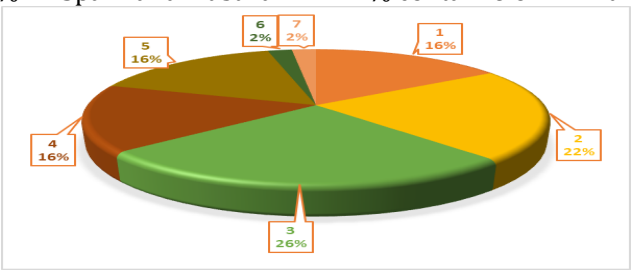

Figure 5. **E-Numbers Count and Percentage in Analyzed Products**

However, by analyzing the average of E-numbers used per product based on the manufacturing country in the products under study, it can be observed that there are countries where the average number of E-numbers used exceeds the figure of 3 (Romania, Italy, Slovenia, France) (see Figure 6).

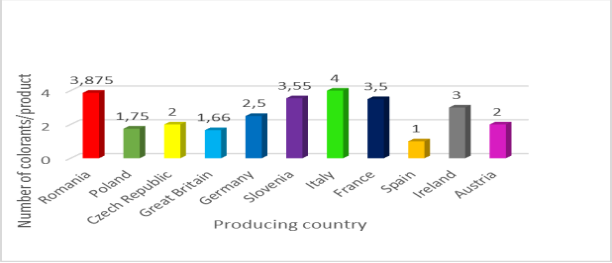

Figure 6. **E-Number Usage in Analyzed Products, by Country of Manufacture**

The pharmaceutical forms in which we most frequently encountered the use of dyes are: capsules at 56% (28 products), tablets at 22% (11 products), lozenges/pellets at 12% (6 products), powders at 8% (4 products), and dragees/coated tablets at 2% (1 product) (see Figure 7).

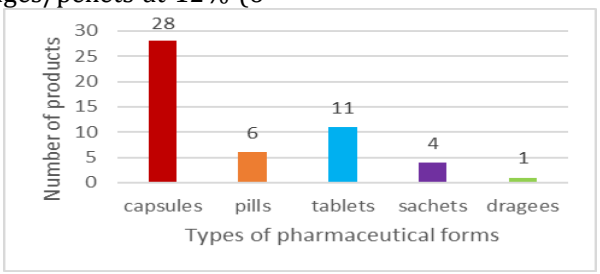

Figure 7. **Types of pharmaceutical forms taken in the study**

The dyes most commonly used as additives from the triphenylmethane, xanthene, and quinoline classes in the formulation of medicines are: E104, E127, E131, and E133.

Among these, the most frequently encountered in the analyzed products was Quinoline Yellow (E104), followed by the triphenylmethane dyes (E131 and E133), and then the xanthene dye (E127) (see Figure 8).

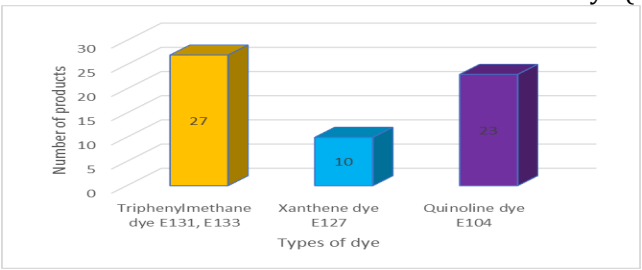

Figure 8. **The most frequently used dyes from the triphenylmethane, xanthene, and quinoline classes in the formulation of the products included in the study**

Dyes from the studied classes were used in the composition of the analyzed medicines: triarylmethane (38.00%), xanthene (17%), and quinoline (45%) (see Figure 9).

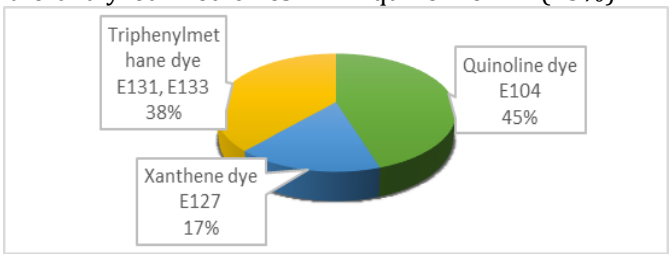

Figure 9. **Percentage of studied dyes used in analyzed pharmaceutical products**

There are numerous studies conducted to demonstrate the toxicity of dyes used in both the food and pharmaceutical industries. Data from the FDA (Food, Drug and Cosmetic Act) show a dramatic, fivefold increase in the consumption of synthetic dyes since 1955 (Potera, 2010).

Reactions induced by products containing triphenylmethane, quinoline, or xanthene dyes vary widely, from nasal congestion or running nose to anaphylactic shock or enterocolitis (Gultekin & Doguc, 2013). Many of these dyes are responsible for causing side effects in children, such as contact dermatitis, gastrointestinal intolerance, bronchospasm, eosinophilia, angioedema, skin rash, and even hyperactivity (Chatterjee & Alvi, 2014; Chequer et al., 2011; Gultekin & Doguc, 2013; Šuleková, Hudák & 2016). Another adverse effect produced by these dyes is their accumulation in the body, which can lead to the delayed onset of cancer (Necula & Babii, 2010; Sandu, 2014; Scientific Committee on Consumer Products, 2005).

Each country maintains its own control regarding the use of additives, in Romania (Ministerul Sănătății, 1998) mandated several regulations: the addition of additives must be labeled on every retail package, the use of food additives is prohibited for the purpose of masking alterations or degradations in food products. Additionally, purity standards that the additives must meet were established (Council, 2012; Mihele, 2008)

CONCLUSIONS

The use of dyes in food and pharmaceutical products carries important implications concerning safety, quality, and consumer perception.

Some artificial dyes can have adverse effects in addition to their benefits, especially in children or sensitive individuals, causing issues like hyperactivity and allergic reactions. Consequently, certain substances have been banned in various countries due to carcinogenic or toxic risks.

Strict regulations govern the use of dyes, both at the national and international levels (e.g., EFSA in the EU, FDA in the USA). Admitted daily intakes (ADIs) are well established, and labeling is mandatory to inform the consumer.

In recent years, an increasing trend has been observed toward replacing synthetic dyes with natural, consumer-safe colorants. However, these natural alternatives have the disadvantage of having lower stability and a higher cost.

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