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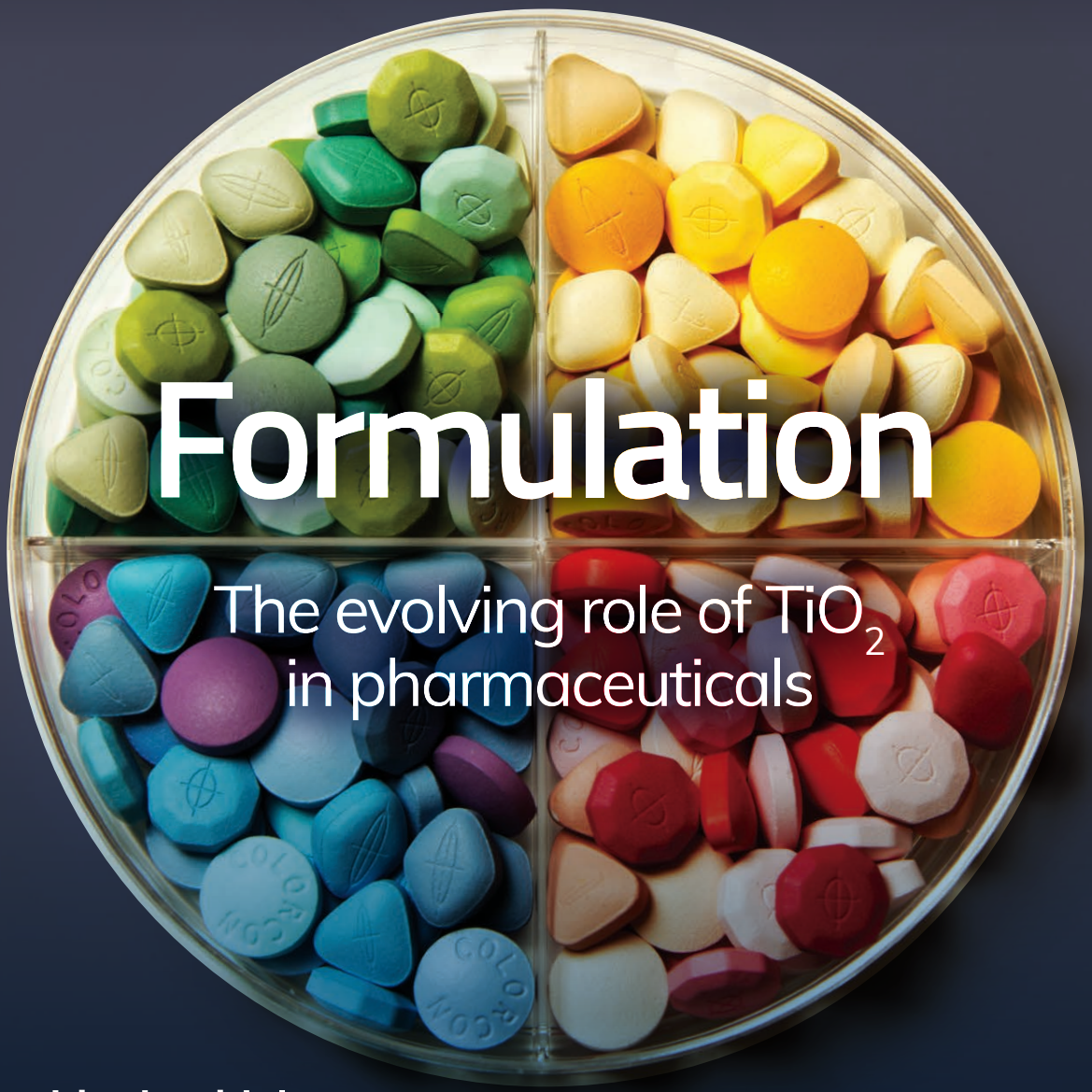

Formulation

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Titanium dioxide (E171) and its role in formulation

In this article Mike Tobyn from Bristol Myers Squibb, Jonathan Kaye from GSK, David Harris from MSD and Eli Lilly's Jason Melnick discuss the role of E171 (titanium dioxide) in the identification of solid oral dosage forms.

THE ABILITY TO uniquely identify oral solid dosage (OSD) forms has been recognised by regulatory authorities worldwide as one of the mechanisms to reduce medication errors and to detect falsified medicines. Changes in the appearance of medicines has been identified as a factor in patient compliance and, therefore, clinical outcomes.

In the development of a new drug product, it is necessary that each dosage form or strength incorporates mechanisms that enable its unique identification. The ability to identify medicines is regarded, in European Medicines Agency (EMA) guidance,[1] as a key mechanism for reducing medication errors: *elderly patients frequently use multiple medicinal products (polypharmacy)*

Figure 1 (left): Examples of tablet colours and shapes that currently allow unique identification of solid dosage forms. As it stands this range is not available using E171-free formulations.

Photo courtesy of Colorcon.

E171, a specific grade of titanium dioxide currently acceptable worldwide in medicines, is a key component of most OSD forms

Figure 2a: Hypromellose capsules opacified without E171.

From left to right: empty / filled with white powder / filled with orange pellets / filled with black pellets.

Photos courtesy of Lonza.

which may in itself cause adherence problems which may be partly overcome by the pharmaceutical design of the medicines used (eg, a wider range of colours, sizes and tablet shapes is known to assist the recognition of medicines and hence to reduce the risk of errors).[1]

Once on the market, unique identification is a key mechanism for helping to prevent and identify falsified medicines. Falsified medicines present significant risks to patients, and their identification and removal is a key goal of healthcare regulators throughout the world.[2] Having unique, difficult-to-falsify features makes the medicines supply chain safer.

Mechanisms for uniquely identifying oral solid dosage forms

As the need to rapidly and uniquely identify a solid oral dosage form is a vital part of product development, several mechanisms to achieve those goals have been endorsed by the pharmaceutical industry and regulators.

1. **Colour** – Many tablets are coated using coloured film coating systems supplied by specialised third party vendors, who provide ready-made systems for reconstitution and coating. These film coats are available in a wide range of reproducible and vivid colours. Batch-to-batch variation is low, and with appropriate colour selection, colour fading with time is minimised. Hard capsule shells are also provided in a wide range of colours or combinations of colours.
2. **Tablet and capsule marking** – Ink printing, where strongly-coloured inks can be printed onto dosage forms, is a regular feature of oral solid dosage forms. Ink lettering can be used to provide unique number/letter and colour combinations. Inks can be of dark colours or light, or bright white, depending on the substrate onto which they are printed. In recent years laser activated printing has developed to become an additional method for identification of OSD forms. With this technology, components of the coat or film can be activated by specific wavelenth of laser light to change colour. The range of features that can be »

The EC is due to re-evaluate by early 2025 the exemption that allows ongoing use of E171 as a colour in pharmaceutical formulations

Figure 2b: Three sets of Hard gelatin capsules with different content. From left to right: (a) opacified with E171; b) with alternative opacifying technology; (c) with calcium carbonate.

In each picture, from left to right: empty / filled with white powder / filled with orange pellets / filled with black pellets.

Photos courtesy of Lonza.

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placed on[3,4] dosage forms by this mechanism is more extensive than for ink printing and is usually employed with newer dosage forms. This technique has been identified as a possible enabler for detection of falsified medicines.[5]

3. **Tablet shape and size** – The ability to visualise and model the shape of a tablet and the mechanisms of compaction within the tablet press has allowed the advance of new unique shapes of tablets, enabling ready identification (and potentially improving ease of use). Modern coating systems with good adhesion to the substrate do not restrict the shape of tablets to the same extent as older coating systems (eg, sugar coating). Furthermore, they allow for more variety in tablet sizes; a feature that is often used to distinguish different dosages of the same drug product.
4. **Debossing** – Tablet debossing is a common technique to identify tablet dosage forms. Generally the nature of the debossing is limited by what can readily be manufactured with a tablet punch, the propensity of a formulation to stick to the punch,[6] and the adherence and bridging of the coating system applied to the tablet. A current approach uses a modern adhesive low solids coat, which has expanded the range of debossing options on the tablet.

Reports of initial solid dosage forms made with the early formulations of E171-free coating systems indicates that some of these systems demonstrate fading over time

The role of E171 as an enabler of dosage form identification

E171, a specific grade of titanium dioxide currently acceptable worldwide in medicines, is a key component of most OSD forms, as it has a unique (in the pharmaceutical armoury) set of properties. These properties allow it to protect the active pharmaceutical ingredient (API) from UV and visible light while being chemically inert; factors which are important in producing a stable product with an appropriate shelf life. E171 can be used in a range of tablet coatings and in capsule shells (of gelatin or hypromellose composition). These exceptional properties are complemented by E171's ability to provide white, bright colour or easily combine with other colourants to create an array of vivid colours and shades. It is highly effective as an opacifier at low solids loading and can be effective in thin coats. These features make E171 an important enabler of unique, visible identification of oral solid dosage forms.

Recently the European Commission (EC) required the removal of E171 from foods intended for sale in the EU. This was not based on an adverse finding of safety with respect to E171, but the absence of a finding of complete safety by the European Food Safety Authority (EFSA).[7] Foods manufactured after August 2022 for sale in Europe cannot contain E171. Uniquely in the EU, only colourants approved for use in food can be used in medicines. Therefore, the EC has further requested that pharmaceutical companies "make all possible efforts to accelerate the research and development of alternatives and replace titanium dioxide in both new and already authorised products". This guidance would affect a majority of the available OSD form medicines in Europe.[8]

Under Regulation 2022/63, the EC is due to re-evaluate by early 2025 the exemption that allows ongoing use of E171 as a colour in pharmaceutical formulations. This will be based on the EMA's re-evaluation (due in Q1 2024) of the impact of E171's removal and the feasibility of alternatives to replace it. Subsequent to the EFSA assessment and the publication of 2022/63, other regulatory authorities have reviewed the safety of titanium dioxide and the EFSA opinion and have indicated that they do not believe any changes to its status in food or medicines are warranted.

As an opacifier (which is different to its function as a colourant), E171 acts as an enabler of the unique identification of dosage forms. The mechanisms for this benefit include:

1. E171 is an important contributor to providing vivid, reproducible colours in tablets and capsules that are resistant to fading. This means that unique colours can be consistently produced and reproduced, and dosage forms made from those colours retain the colour throughout their product life.
2. E171 is a key component of printing inks used to identify tablets and capsules. It is the key element of white inks but is also used in darker ink systems, with the colour and opacity of the ink selected to provide contrast with the tablet or hard capsule shell. E171 has the unique property, among the compendium of pharmaceutical materials, of undergoing a reproducible colour change on specific excitation by laser light – a technology being used in an increasing number of dosage forms.
3. As a facilitator of thin, adhesive films, the tablet shapes that can be accommodated within the coating range of tablets has grown significantly in recent years, which means that dosage forms can be rapidly identified by shape. Likewise, its ability to induce opacity at relatively low solids content permits manufacturing of robust capsules in a range of sizes, independent of the base material.
4. Debossing. The thin films possible with E171-based coatings allow modern pharmaceutical coats (which are largely

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based on PVA or hypromellose) to adhere to tablet substrates, which increases the range of shapes and lettering that can be used for embossing and identification.

Alternatives to E171 in tablet coatings and hard capsule shells

If E171 is removed as an option for inclusion in OSD forms, it is important that any alternative retains as many of the properties outlined above as possible to maintain the uniqueness of these dosage forms. In addition, it would be preferable for any alternative to be inert and usable in the same settings as are currently deemed suitable for formulations containing E171. As it stands, none of the materials currently identified as potential replacements have the ability to block UV to the same extent as E171, and have a significantly lower refractive index than E171,[9] implying that like-for-like replacement will not be possible. This puts the UV protection provided by E171, and the colour and hiding capacity provided by the tablet coat or capsule shell, at risk.

Initial colour palettes provided by suppliers indicate that the range of colours possible using currently identified replacements is different from that currently available using E171; thus colour matching with current presentations may not always be possible. The palette may have a sufficient range of colours for new medicines, but colour matching with the current systems may be difficult to achieve. This could be significant when trying to replace E171 in medicines already on the market.

At a recent APV conference on the challenges relating to the replacement of E171, reports of initial solid dosage forms made with the early formulations of E171-free coating systems indicates that some of these systems demonstrate fading over time. Data also indicates that the new coating systems, which either need a higher solid content or a longer application time, do not adhere to the dosage form as well as E171-based formulations. There can also be a lack of visual colour uniformity on the tablets, particularly on the sharp edges of the dosage form. These complications of using E171-free coatings systems may end up narrowing the ranges of possible tablet shapes and debossed features.

Recent innovation with alternative opacifying technologies demonstrates that equivalent whiteness and light protection in the capsule could be achieved with materials other than E-171, but these solutions are not fully developed and do not currently have regulatory clearance.

New printing inks are being developed to replace those containing E171, to replicate the identification function for dosage forms, but not all colours currently on the market can be replicated yet, and white inks will remain a specific problem. There is currently no alternative identified that allows for the laser activation of the material as an identification mechanism for the dosage form.

Innovations in the market are inevitable and welcomed. However, a timeline for their introduction to meet potential delisting of E171 will need to be developed and agreed by the industry and regulators since the feasibility, as direct replacements of E171-free colour mixtures and capsule shells has not been confirmed at this stage.[10]

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> *New printing inks are being developed to replace those containing E171, but not all colours currently on the market can be replicated yet*

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