Product Development

PQRI Workshop:
TiO2 Use in Pharmaceuticals
Global Regulatory and Technical Challenges
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Overview of Pharmaceutical Uses of TiO2 and technical challenges with use of Alternatives

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Outline presentation

- Present technical details of E171 and alternatives
  - What is E171
  - What properties does E171 have?
  - How is E171 used in oral solid dosage forms?
  - What properties do potential alternatives have?
  - What are the consequences of replacing E171 with alternatives?

What is E171?

E171 is a grade of titanium dioxide which meets standards for food

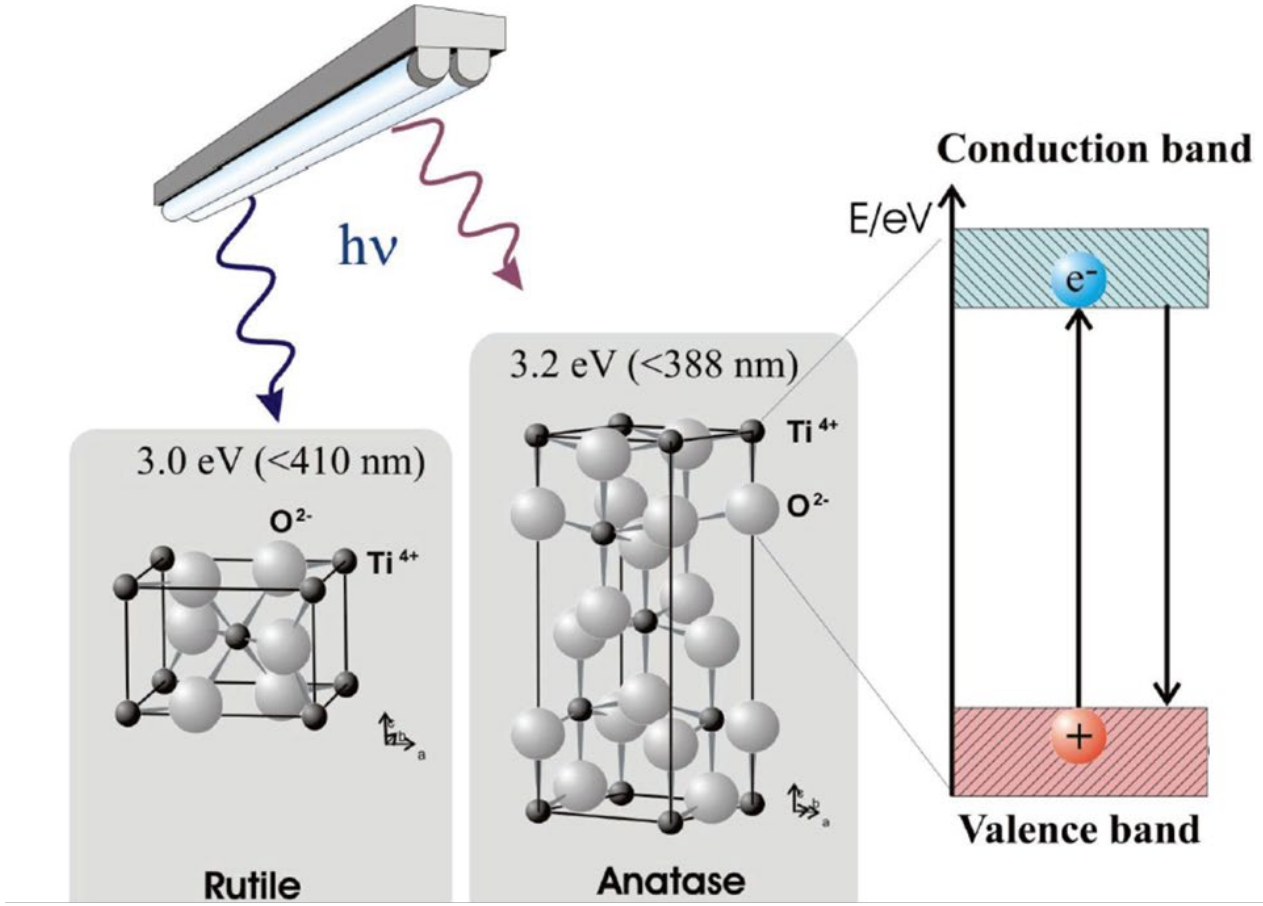
- E171 is a synthesised, powder grade of titanium dioxide
  - Titanium dioxide occurs naturally in a range of crystalline forms, and non-crystalline forms.
- E171 is produced by a specific manufacturing route, the sulfate process, and produces a specific material
  - Made from ilmenite ores, via a specific manufacturing route with lower use of adjuncts
  - Lower yields but more acceptable product due to lower use of adjuncts
- If the relevant food and quality standards are met, E171 can be used in food and pharmaceuticals
  - Pharmacopoeially listed in major markets
- E171 is approved as a colorant for foods in many countries, and was listed as a food ingredient in Europe until recently

General Properties

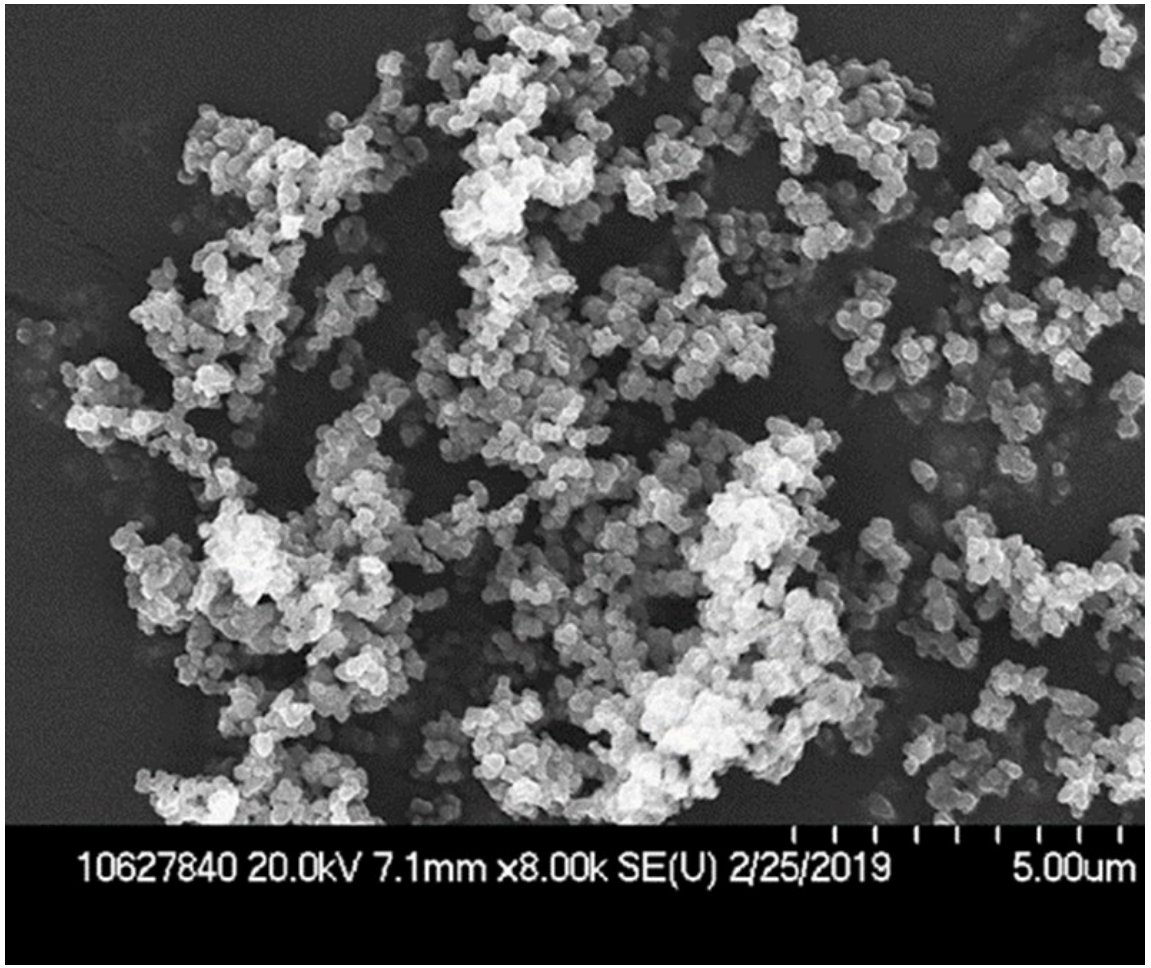
- High stability/low reactivity
- Low solubility
- Physically stable under pharmaceutical use
- White
- Lustrous
  - Provides definition and lustre for almost all paints, of whatever colour, and other colorant activity
- Particle size ideal for blocking visible light

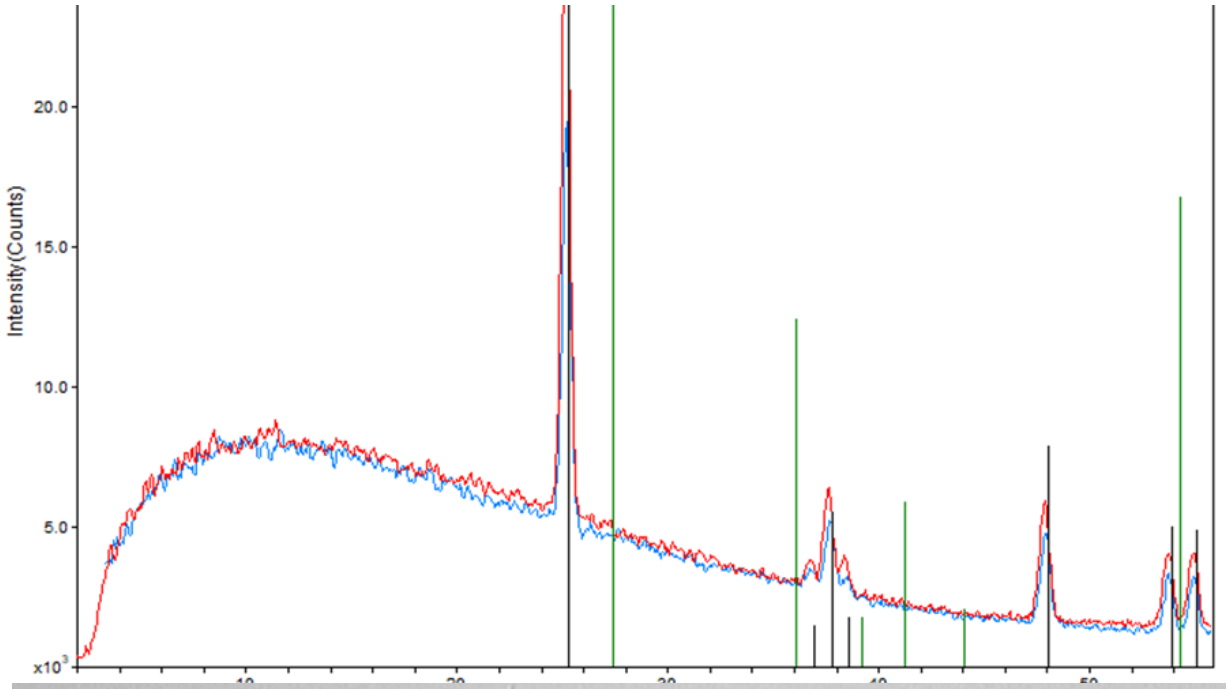
Absorption of UV Light – semiconductor

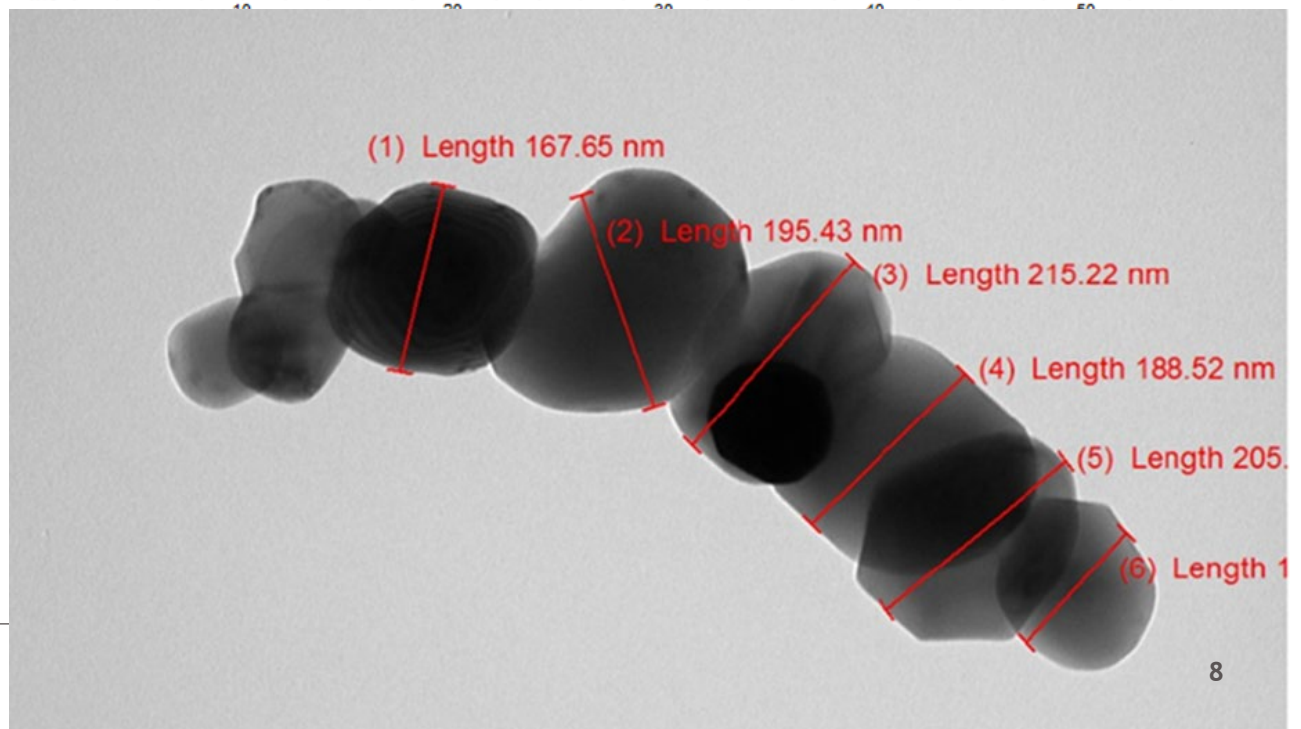
- Absorption of UV promotes an electron from the valence band to the conduction band



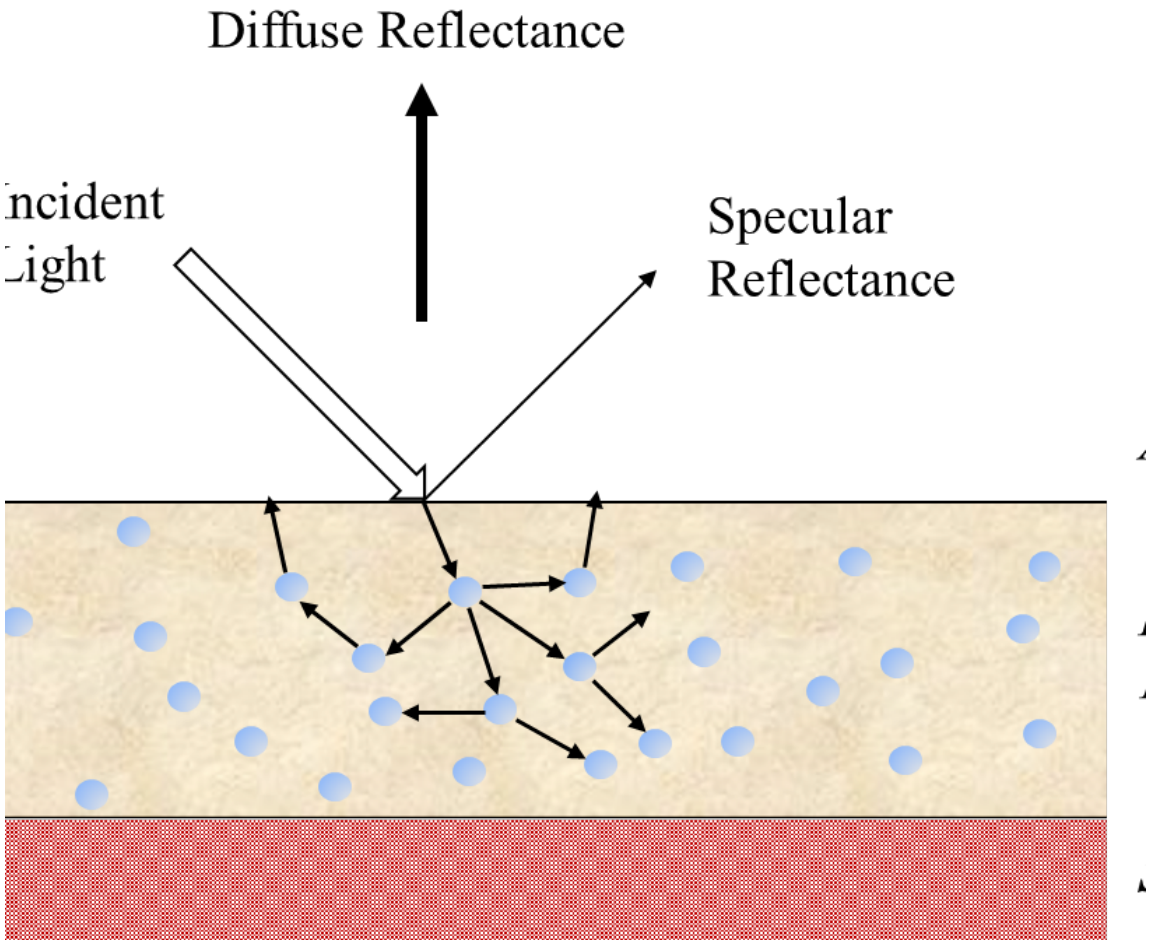
Physical form of E171

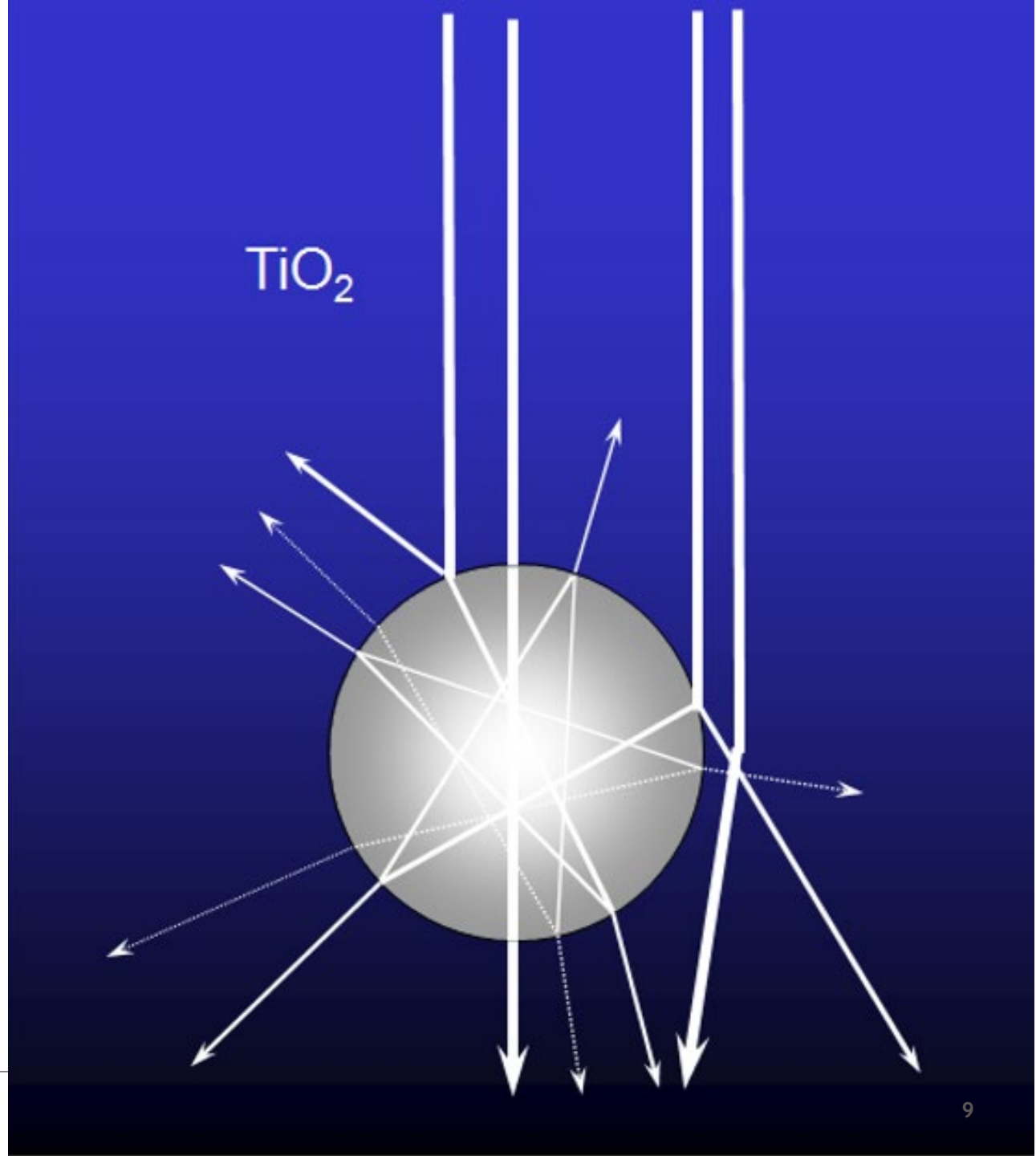




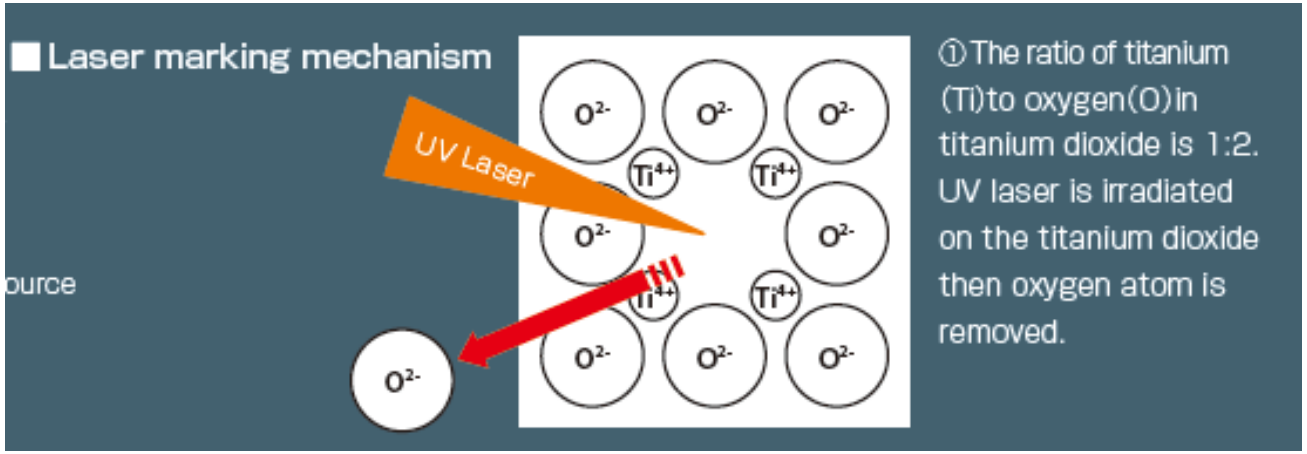


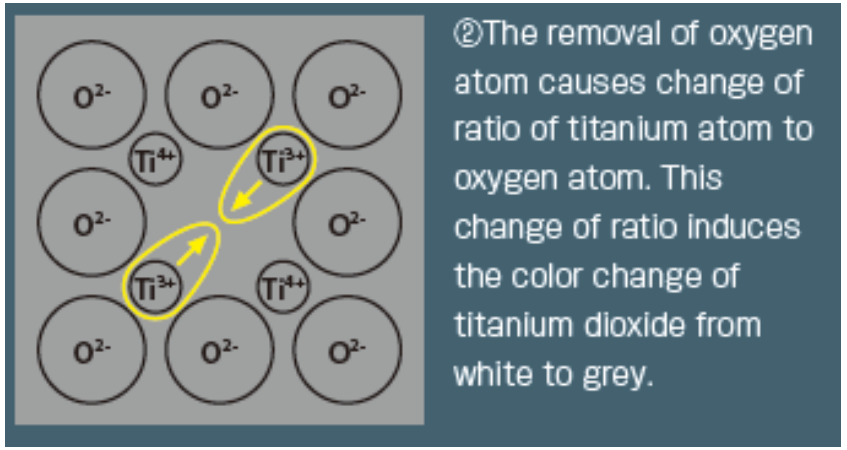
Opacity – high refractive index and multiple particles
SEPARATE Property from UV absorption





Photochemical Reaction and color change on irradiation





How is E171 used in oral solid dosage forms?

Used in films coats and capsule shells

- E171 is used in a large majority of all oral solid dosage forms in film coated tablets and in capsule shells
  - 66% of all OSD's in Europe
- Provides protection for medicines, and does not disrupt other protective effects
  - UV and visible light blocking
- Provides mechanisms for unique identification and batch to batch consistency
- Is being increasingly used for on product identification and anti-counterfeiting measures
- Provides easy to swallow, smooth finish.

Coloring And Shape

How do we help patients by uniquely identifying dosage forms?

- Reduce risk during manufacture(product mix up)
- Reduce risk of falsified medicines
  - Rapid identification of falsified medicines
- Reduce risk of misadministration
- To identify dosage forms in case of emergency

Visionary Applications of UV Laser Printing

Broaden strategies for

- Product identification
- Anti-counterfeiting

Very flexible

How much E171 is required to achieve these effects?

Film coated tablet calculation	Typical minimum	Typical maximum
Tablet weight (mg)	75mg	1000mg
Film coating weight gain (%)	1%	5%
Film coating weight gain (mg)	0.75mg	50mg
TiO2 content of film coat (%)	10%	30%
TiO2 content of film coat (mg)	0.075mg	15mg
Approximate TiO2 content per tablet	**0.075mg**	**15mg**

What properties do potential alternatives have?

Current evidence - materials science perspective

- All currently identified materials are not as technically efficient as E171 (published and unpublished work)
  - Work has rightly focussed on approved ingredients
  - Path for novel materials exceeds the timelines required
- Lower protection from UV
  - Do not absorb UV light via bandgap mechanism
- Lower refractive index
  - Less hiding power
  - Do not provide definition to colour
- No capacity for laser activation

Many proposed alternatives have other liabilities

- May be mined directly
  - Nitrosamines and contamination
  - At least one is talc
- The particle size issue and efficiency are intrinsically linked
  - Without nano dimensions materials are likely to be much less efficient in blocking visible light
    - A particle size of x2 the wavelength is most efficient
    - E171 has dimensions less than 1µm but not less than 100nm, which means that it is not a nanomaterial by this definition.
  - Many alternatives are on the original list which listed titanium dioxide as a risk, leading to its delisting
- It is not clear whether these materials could meet the needs of the pharmaceutical industry
  - Supply chain robustness and redundancy
  - Capsule supply

What are the consequences of replacing E171 with alternatives?

How much of the alternatives will be required?

- The alternative materials will have to be administered at significantly greater levels to achieve what they are capable of
  - No equivalence will be achieved in some cases.
    - Colors, printing and shape could change
  - These greater levels could have effects on moisture and enteric coatings
    - Higher solids content of larger particle size
  - Will change several characteristics of the dosage form

Consequences of replacing E171 in capsules and tablets

- All formulations will require an **extensive** reformulation, revalidation of production and analytical methods
  - Consequences for the stability of the product
    - Protection from UV light
    - Effect of extended processing on stability
    - Loss of patency for moisture and enteric coats
    - Stability and protective effects of capsules could be lost
  - The tablet size and colour may change, other identifying features may also
    - Implications for packaging and stability
- The manufacturing consequences have not been defined
  - Will capsules with higher solid loads be as robust in at scale manufacture
  - Will processing equipment need to be modified (coaters, encapsulation)

Consequences of replacing E171 in capsules and tablets - 2

- Reformulated products will have to be refiled and reapproved
- An education programme for patients will be necessary
  - Accept colour change and variability
  - Professional support (Carers, Pharmacists) may be necessary after training.

Consequences of alternate materials

- Coats/shells may be required to be thicker
  - Exposure of drugs to adverse conditions may be greater
  - Processing times will be higher
    - Tablet breakage may be higher or shape will have to change
  - Tablet shape could change (and colour matching may not be perfect)
    - Effect on packaging and patient acceptance
- Solids contents of coats and capsules will be higher
  - Consequences for physical properties of coats, and protection from moisture and light

Almost all mechanisms for anti-counterfeiting, identifying and branding tablets are significantly impacted

- Loss of colour palette
- Batch to batch variation will become greater
- Thicker coats will mean loss of definition for logos, and change in shape of tablet
- Ink printing may not be feasible (inks contain titanium dioxide)
- ← Laser activation of titanium dioxide will be lost

In Summary

- E171 is included in a majority of solid oral dosage forms, and has been present in them for many years
- Of approved excipients it has unique functionality, and high stability/low reactivity
- Replacement materials cannot match the performance of E171 and will be required to be used in greater amounts in different ways
  - And MAY not have the same track record of safe use
- This will necessitate reformulation of products with knock on implications for manufacturing, packaging and registration
- Many proposed alternates have the same liabilities as E171
  - Or have liabilities that might emerge with equivalent scrutiny to E171

Acknowledgements

- IPEC Europe and IPEC Americas
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The Role of Titanium Dioxide (E171) and the Requirements for Replacement Materials in Oral Solid Dosage Forms: An IQ Consortium Working Group Review

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