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Short communication

Challenges of possible replacement for titanium dioxide in Dapoxetine film coating tablets

Ana Smileva*, Natalija Dimovska, Biljana Keleshovska, Dobrinka Dimova, Liljana Makraduli

Replek, Kozle 188, 1000 Skopje, North Macedonia

Introduction

Titanium dioxide (TiO_2) is naturally occurring mineral widely used in many industries as an inert substance giving consistent homogenous colour. It is also an opacifying agent, which protects the photosensitive ingredients from light degradation and extending the shelf life of the product.

Recently, European Food Safety Authority (EFSA) declared that TiO_2 could not be considered safe for use as a food additive, despite scientific findings and data on nanoparticles. This is due to genotoxicity, possibly carcinogenic properties to humans and accumulation in the body due to their long half-life.

Although the ban impacts products designated as food, there is currently no requirement to remove TiO_2 from pharmaceuticals. European Medicines Agency (EMA) should apply a pragmatic approach in their evaluation on the use of TiO_2 in the European Union/ European Economic Area (EU/EEA) to ensure product availability and patient supplies (AESGP, 2021).

There is no guarantee that a replacement of TiO_2 can be appropriate for every product and it would result in "significant medicine shortages" or withdrawals from the market (Taylor, 2021).

TiO_2 is monographed in the European Pharmacopoeia and it is considered as suitable for use in the medicinal products as an excipient. While other excipients could also be used for the same purposes in tablet coatings, TiO_2 has unique properties enabling thinner, less brittle film coating and allowing rapid bioavailability of the active substance (EMA, 2021). Possible identified alternatives (e.g. carbonates, starches, phosphates, talc) or removal of TiO_2 from the composition without replacement, are not identified with comparable properties in regards to whiteness, refractive index and inability to obtain sufficiently thin films, and impurities risk.

It is expected that medicinal products will require case by case approach in designing TiO2 free coating formulations, since no other excipient could directly replace it in all its properties. Each product will have to be evaluated on its characteristics, exposure level and extensive studies will need to be conducted to understand the feasibility of removing or replacing TiO_2.

The aim of this research was to use film coating without titanium dioxide for Dapoxetine film coated tablets in order to evaluate the possibility of replacement of titanium dioxide with another excipient.

Materials and methods

Materials

Tablet core contains: Dapoxetine hydrochloride, "RL Chemicals", India; Lactose monohydrate: Tablettose®80, "Meggle", Germany; Croscarmelosse sodium: Vivasol®, "JRS Pharma", Germany; Microcrystalline cellulose: Vivapur®12, "JRS Pharma", Germany; Magnesium stearate, "Mosselman", Belgium and Sillica, colloidal anhydrous: Cab-o-sil, "Cabot" USA.

Film coating contains: Opadry®Grey 03F275002, "Colorcon", Germany (Hypromellose, Titanium dioxide (E171), Macrogol 6000, Iron oxide black, Iron oxide yellow, Talc) and Opadry®Grey Titanium Free (TF) 265F275003, "Colorcon" Germany (Hypromellose, Calcium carbonate, Macrogol 6000, Iron oxide black, Iron oxide yellow).

*ana.smileva@replek.mk

Methods

The active substance and the excipients are sieved and mixed together. Tablets are produced on tablet press, "Erweka", type EK O, Germany by direct compression. Tablet cores are divided in two equal parts for film coating on the machine, "O'Hara Technologies", type Labcoat M, Canada with 5% weight gain on perforated coating pan. Titanium dioxide and Titanium dioxide free aqueous suspensions are prepared with 15% solid materials. The film coating process is performed with the same parameter values of inlet airflow and temperature, spray rate, pan speed and atomizing and pattern air pressure. Dissolution study is performed with UV-Visible spectrophotometer "Shimadzu", type UV-1800, Japan (Ph. Eur. Apparatus 2 paddle).

Results and discussion

The dissolution results for both trials are comparable and within the requirements and limits of tolerance (minimum 75% Dapoxetine as hydrochloride expressed as a percentage of the declared content dissolved for 30 minutes). The appearance of film coated tablets is similar, with no significant difference of the grey colour of the film coating. Since, there are no direct alternatives to TiO_2 with the same opacifying and pigment properties, in many cases colours of TiO_2 free formulations are brighter.

Stability study will be conducted in different packaging and different conditions to support the changes of the product composition and establishing the appropriate shelf life for the formulation. This is initial data and the study will show if there will be colour change and development of impurities in the future. Alternate coating formulations may not exhibit the same film coating tablet strength, so bulk stability studies for possible tablet hardness changes also can be performed.

To achieve the same or similar level of opaqueness, manufacturers would likely have to use larger amounts of other colorants (AESGP, 2021). Alternatives, especially if used in larger amounts, could have greater incompatibility with active substance or other excipients.

Development steps are necessary to be taken for good manufacturability, stability and clinical performance. Compatibility of the new excipient(s) with the active substance(s) and with any other excipient is important to be demonstrated in tablets and binary mixtures. Also, a photostability study should be performed.

Conclusion

The feasibility of replacing TiO_2 cannot be confirmed at this stage. Each affected medicinal product will need an individual review and assessment, which will require investigation of other alternatives, product reformulation, and generation of new data related to manufacture, stability testing and potentially new clinical and bioequivalence studies which subsequently will all have to be assessed by the national competent authorities and EMA. The EC will review the continued use of TiO_2 in medicinal products within three years after the date that the amendment to Regulation (EC) No 1333/2008 concerning the food additive E171 comes into force. The EC review will be based on an updated assessment by EMA, performed before 1 April 2024 (EC, 2021).

An acceptable transition period in all specific uses in medicines covered by the scope of the colouring materials is currently difficult to predict or estimate. Time needed to reformulate each individual product could take several years depending on the formulation and studies required, followed by the necessary regulatory procedures for assessment and approval. Pharmaceutical industry should make any possible effort to accelerate research and development alternatives, to replace TiO_2 in both new and already authorized products and to submit the necessary changes to the terms of marketing authorizations concerned.

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