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Short communication

The importance of compatibility studies in selection of appropriate TiO_2 free non-functional film-coating for solid dosage formulation with antioxidant

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Introduction

This short paper aims to present the importance of compatibility studies of API/Excipient with film-coating mixtures containing alternative material to TiO_2 (specifically $CaCO_3$) intended for film-coating process of tablets as one of the most used solid dosage forms.

Titanium dioxide is one of the most commonly used excipients in the pharmaceutical industry in oral solid dosage forms. This excipient is wide known as a strong white pigment and opacifier in film-coating materials and capsule shell coloring (Sheskey at al., 2020). The ability to disperse light as a function of the natural properties of a polymorph form known as anatase of commercial titanium dioxide provides opacity, enhancing contrast, protection from photolytic degradation and smoothness of the resulting product (EMA, 2021). All of the above-mentioned roles make this excipient unique and hard to replace in the technology process of film-coating of pharmaceutical solid dosage forms. However, in recent years, based on some available evidence data (Bettini et al., 2017) it is stated that titanium dioxide particles have the potential to induce DNA strand breaks and chromosomal damage and furthermore might lead to formation of aberrant crypt foci. These concerns led to European Medical Agency (EMA, 2021) providing an analysis with aim to define the feasibility of alternatives to replace it without impacting the quality of medicines and more important their safety and efficacy. The alternative material has to meet the following expectations: chemically compatible with other excipients; suitable opacifying performance at low dosage levels; environmentally sustainable; economically viable; easily processable with conventional equipment for pharmaceutical manufacturing. There are many different commercial ready-to-use film-coatings with possible alternatives to titanium dioxide containing calcium carbonate, talc, starch, zinc oxide, calcium phosphate, dicalcium phosphate etc. (AESGP, 2021) However, most of them have a refractive index significantly lower than titanium dioxide anatase form which means that will require greater (w/w)% equivalent to spread light to the necessary degree, therefore their use presents a challenge in the pharmaceutical industry (Blundell et al., 2022) Based on the current available literature data (Radtke et al., 2021) regarding effectiveness none of the aforementioned alternative pigments show results similar to TiO_2. Most of the commercially available ready-to-use film-coating mixtures include $CaCO_3$, which is the main reason for the focus of this short paper - to present the importance of chemical compatibility of API/EXP and $CaCO_3$ as one of the most used alternative materials to TiO_2.

Materials and methods

The aim was to investigate the compatibility between the ascorbic acid used as an antioxidant in solid dosage formulation and TiO_2 free PVA-PEG based film-coating materials, one with and the other without $CaCO_3$. Two binary mixtures were prepared with ascorbic acid and the film-coatings with the same ratio (Ascorbic acid: Film-coating 1:10). One binary mixture was prepared with Ascorbic Acid and Calcium Carbonate in 1:1 ratio.

Binary mixture 1 was prepared by dry mixing of Ascorbic Acid 97% and ready-to-use TiO_2 free PVA-PEG based film-coating mixture containing calcium carbonate as alternative material to TiO_2. Binary mixture 2 was prepared by dry mixing of Ascorbic Acid 97% and ready-

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to-use TiO_2 free PVA-PEG based film-coating mixture that does not contain calcium carbonate in its formulation. Binary mixture 3 was prepared by dry mixing of Ascorbic Acid 97% and Calcium Carbonate.

Samples were dispersed in Petri dishes and kept for 30 days in stability testing chambers at temperatures of 25 °C with a relative humidity (RH) of 60% (binary mixture 1;2) and 40 °C with a relative humidity (RH) of 75%. (binary mixture 1;2;3)

The solid-state compatibility study of ascorbic acid and TiO_2 free film-coating mixtures was performed with scientifically sound approach using Fourier Transform Infrared (FT-IR) spectroscopy. The compatibility was studied by comparison of the FT-IR spectra of the prepared binary mixtures.

Results and discussion

Comparison of the FT-IR spectra and organoleptic evaluation of the samples, initially and after exposition on the above-mentioned conditions, has been done.

After organoleptic evaluation on Binary mixture 1 kept at 40 °C/ 75% RH were confirmed some visual changes, more specifically, dark brown to black pigments were manifested everywhere across the binary mixture. Moreover, the FT-IR spectra data presented appearance of new bands in the FT-IR spectrum, non-typical for the described excipients which is considered as significant sign of possible solid-state interaction and formation of new molecular species.

Binary mixture 3 at the same conditions (40 °C/ 75% RH) also showed significant visual change with noticeable dark pigmentation across the mixture.

Calcium carbonate is known to react with ascorbic acid in a stoichiometric ratio of 1:2 and form one of the widely known metal ascorbate salts-calcium ascorbate. The reaction is presented with the formula: $CaCO_3 + 2C_6H_8O_6 \rightarrow C_{12}H_{14}CaO_{12} + CO_2 + H_2O$. Under stress conditions, calcium ascorbate can exhibit thermal decomposition characterized with physico-chemical changes including dark pigmentation. To further investigate if this particular interaction is the cause of the aforementioned chemical incompatibility, the FT-IR spectra from binary mixture 3 was compared with the spectra from binary mixture 1. The obtained spectra indicate that calcium carbonate probably reacts with ascorbic acid and forms calcium ascorbate that can easily decompose under higher temperature. Therefore, it cannot be used as alternative material to TiO_2 in film-coating mixtures intended for film-coating process of tablets compressed from final blend in which ascorbic acid is incorporated. Even though this excipient according to the literature data and manufacturers claims is offered as a strong white pigment, alternative to TiO_2, its especially chemical, but also physical compatibility-possibility of color change is of great importance for selection of the appropriate TiO_2 free non-functional film-coating for solid dosage formulations.

Conclusion

At the time of writing, TiO_2 free film-coatings are relatively new in the pharmaceutical industry. The available alternative ready-to-use film-coating mixtures introduce components that can interact with the active ingredient or excipients and impact the physical and chemical stability of tablets. According to the above-mentioned it is highly recommended to include these materials in the compatibility studies as part of the pre-formulation phase. In conclusion, the search for replacement of titanium dioxide is a popular challenge in the pharmaceutical industry mainly for research and development scientists, because of the limited timeframe for development and moreover because of the complexity and limited experience regarding this particular situation.

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