INTERNATIONAL JOURNAL OF PHARMACEUTICAL EXCIPIENTS

Concerns regarding Calcium Carbonate as an alternative Excipient for Titanium Dioxide

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Received: February 10, 2025; Accepted: February 26, 2025

Opinion and Commentary

ABSTRACT

Titanium dioxide (TiO_2) is widely used in pharmaceutical film coatings and capsule shells, with its white color and opacity used to improve the appearance of drug products and enhance the chemical stability of certain drugs. The European Commission banned the use of TiO_2 in foods in Europe and the ban may be extend to include pharmaceutical products. Calcium carbonate ($CaCO_3$) is an excipient that is being used as an alternative to TiO_2 in the nutraceutical/dietary supplement industry. This excipient, however, is a basic compound that has the potential to affect drug stability. Moreover, the calcium in the calcium carbonate can complex with certain drugs. This paper considers these two issues and proposes that both compatibility and bioavailability studies may be needed when replacing TiO_2 in pharmaceutical products with calcium carbonate.

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INTRODUCTION

Titanium dioxide (TiO_2) is an insoluble white pigment that has been used in the pharmaceutical industry for over 50 years (1). Its ability to scatter light makes TiO_2 a powerful opacifying agent. TiO_2, along with the aluminum lakes of water-soluble dyes and the iron oxides, are generally included in pharmaceutical coatings and capsule shells to improve the aesthetic appearance, provide for product identification, minimize medication dispensing errors, improve drug stability, and reduce counterfeiting (2–9). TiO_2 is also used as white pigment in pharmaceutical inks and UV laser printing (10).

In 2002, the European Commission banned the use of TiO2 as a food additive in the European Union due to concerns related to genotoxicity (11,12) and there is a potential for that ban to be extended to pharmaceutical products (13). Given the importance of TiO2 in pharmaceutical products, alternative excipients have been investigated by excipient suppliers, pharmaceutical companies, and some academic researchers (1). Regardless of which alternative is used, these excipients should not adversely affect drug stability or bioavailability.

Calcium Carbonate as an Alternative Opacifying Excipient

One of the most commonly used alternative opacifiers in both capsules and coatings is calcium carbonate (14, 15). Researchers have shown that thicker polymer films (higher coating weight gains) were required to achieve a degree of opacity approaching that of TiO_2-containing films (1, 14, 16, 17). However, the opacity achieved was insufficient to protect photolabile drugs from degradation (1, 16, 17). Nonuniform color, particularly at the land area or edges of coated tablets, have also been reported with calcium carbonate (1).

Risk of Interactions between Calcium Carbonate and some Active Pharmaceutical Ingredients (APIs)

While calcium carbonate is listed as an opacifier in the Handbook of Pharmaceutical Excipients, it is also characterized as a buffering agent (18). Indeed, calcium carbonate is the active ingredient in some antacid tablets. Blundell et al (15) suggested that compatibility studies would be needed with calcium carbonate because of the potential to change local pH of the dosage form. Hancock et al (1) also suggested that the presence of such inorganic salts could cause chemical incompatibility, depending on the drug substance and fill excipients.

Base-Mediated Hydrolysis

Drugs can contain chemical groups that can undergo base-mediated hydrolysis (such as esters or amides) and calcium carbonate could accelerate their degradation, resulting in shorter shelf life. Examples of drugs containing esters include aspirin and simvastatin whilst beta-lactam antibiotics and rivaroxaban represent drugs containing amides. Although Snape et al (19) provides an overview of how the chemical structure of different esters and amides impacts their susceptibility to undergo hydrolysis, such degradation cannot be predicted accurately. Therefore, compatibility studies will be needed to reevaluate the shelf life of drug products containing hydrolysable functional groups when replacing TiO_2 in pharmaceutical products with calcium carbonate.

Complexation with Certain Drugs

TiO_2 is not capable of dissociation under any pharmaceutically-relevant conditions and so interactions of its components (such as Ti^{4+} ions) with other components in a dosage form, including the active ingredient, does not occur. However, calcium carbonate is capable of dissociation, forming Ca^{2+} in water, and these polyvalent cations can complex/chelate a range of drugs. For example, it is well-known that Ca^{2+} strongly complexes with the entire drug classes of tetracyclines, fluoroquinolones, and HIV-integrase inhibitors (20–23) and some cephalosporins (24), while there are individual cases of such complexation in many other drug classes (25). Indeed, in pharmacy practice, instructions are provided to patients to not to take these medicines with dairy products (due to their Ca^{2+}) to prevent complexation.

As calcium carbonate-containing film coatings or capsules dissolve, Ca^{2+} ions will be in intimate proximity with solvated drug and thus there is a potential for complexation to occur in the gastrointestinal tract. Such complexation can reduce drug bioavailability (22-24), which can be particularly serious in the case of anti-infective drugs, leading not only to failed therapy but the potential development of antibiotic-resistant organisms through sub-optimal antibiotic exposure. In the following examples, we examine how much drug

could complex with Ca^{2+} from calcium carbonate using minocycline as an example.

The reported stoichiometry of Ca^{2+} binding with minocycline is dependent on pH, with 1:2 complexation at pH 6.8 and a 1:3 ratio at pH 7.5 (20). In this first scenario, we consider coating a tablet with an immediate release polymer. Since the exact amount of excipients in ready to use film coating materials is not publicly available, we made the following assumptions based upon our experience and the literature. First, we assumed a tablet weight of 250mg. We also assumed a concentration of 25% w/w calcium carbonate (based on total dry weight of the coating material), as this was the concentration Galata et al (16) used in their experiments. We then calculated the amount of calcium carbonate present if coating weight gains were 5% or 7%, as both Galata (16) and Radtke (17) used these weight gains in their experiments. The available strengths of minocycline are 50, 75 and 100 mg, which is equivalent to 109.3, 163.9, and 218.6 μmols, respectively. We calculated the amount of calcium present in a film coating at either 5 or 7% weight gain and determined the percentage of minocycline that could be complexed at pH 6.8 and 7.5. These values are reported in Table 1.

It can be seen from Table 1 that the potential for complexation of minocycline by calcium carbonate is quite high, ranging from 29% (highest dose, lowest coating weight gain, and pH 6.8) to 100% (lowest dose, highest coating weight gain, and pH 7.5). Moreover, if a tablet weighed more, the percentage of drug complexed would be even higher as more calcium ions would be present.

While we modeled complexation based on limited data published regarding film coating formulations, information about the amount of calcium carbonate used in capsule shells is even more scarce. Thus, for the second scenario, we calculated the amount of calcium carbonate needed to complex 25% of the dose of minocycline. As can be seen in Table 2, the amount of calcium carbonate needed is dependent on the dose of the drug as well as the pH, ranging from 1.36 to 2.72 mg at pH 6.8 (2:1 drug:Ca^{2+} ratio) and 0.91 to 1.82 mg at pH 7.5 (3:1 drug:Ca^{2+} ratio). Thus, the presence of even small amounts of calcium carbonate in capsule shells could complex a significant percentage of the drug.

The above calculations were simply based on stoichiometry. While such complexation would likely affect drug bioavailability, other factors could impact Ca^{2+} complexation that our calculations did not take into account. For example, the presence of food or other components in the gastrointestinal fluid such as proteins and surfactants as well as the excipients in the dosage form may impact calcium complexation. In addition, the association and dissociation rate constants of drug-Ca^{2+} complexation have not been reported and there may be other sources or sinks of calcium. A full

Table 1. Potential minocycline complexation with either 5% coating weight gain at pH 6.8 or 7% weight gain at pH 7.5.

Minocycline Dose	μmols Ca^{2+}		Potential Minocycline Complexation	
	5% weight gain	7% weight gain	At pH 6.8 and 5% coating weight gain	At pH 7.5 and 7% coating weight gain
50 mg (109.3 μmols)	31.2 μmols	43.7 μmols	57 %	100 %
75 mg (163.9 μmols)			38 %	80 %
100 mg (218.6 μmols)			29 %	60 %

Table 2. Amount of calcium carbonated needed to complex 25% of the dose at pH 6.8 or 7.5.

Minocycline Dose	Amount of Calcium Carbonate Needed to Complex 25% of the Dose	
	At pH 6.8	At pH 7.5
50 mg (109.3 µmols)	1.36 mg	0.91 mg
75 mg (163.9 µmols)	2.05 mg	1.37 mg
100 mg (218.6 µmols)	2.72 mg	1.82 mg

understanding of these variables is required to model or predict the extent of complexation and its potential impact on bioavailability. Moreover, for drugs that are preferentially absorbed in the upper region of the small intestine, the kinetics of association and dissociation could further impact drug absorption and bioavailability as drug-Ca^{2+} complexes may be transported beyond the absorption site.

CONCLUSIONS

Overall, reformulating TiO_2 with calcium carbonate is unlikely to be a simple task of swapping one excipient for another. Rather, calcium carbonate may impact the stability of certain drugs, necessitating *in vitro* stability studies. Importantly, the ability of calcium to dissociate from calcium carbonate and complex with certain drugs may also affect bioavailability. Due to numerous variables, modeling complexation may not accurately predict bioavailability. Therefore, *in vivo* bioavailability studies will likely be required with a risk of bioequivalence to the original product not being achieved.

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