eye on excipients

Javier Camargo and Carolina Diaz Quijano
Omya

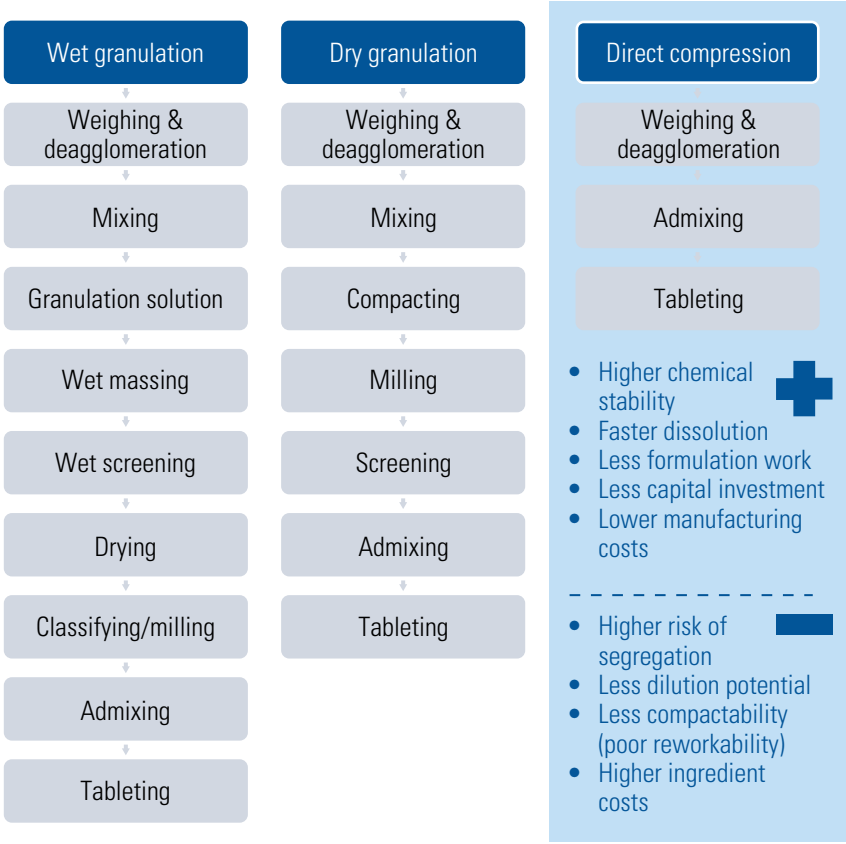
This edition of "Eye on excipients" discusses the pros and cons of direct-compression tableting and describes a study conducted to test the benefits of adding dry binders to direct-compression tablet formulations.

Compressed tablets continue to be the most popular pharmaceutical dosage form [1]. They provide higher content uniformity and are easier to administer at home than syrups or suspensions. They also provide superior chemical, microbiological, and mechanical stability when compared to other solid dosage forms, such as lyophilized tablets. Additionally, compressed tablets are the most cost-efficient dosage form, as they are easier to transport and store than other forms and can also be designed for fast disintegration (ODTs) and immediate, delayed, or targeted drug release.

Compressed tablets can be made using a wet-granulation process followed by compression or simply by direct compression (DC). DC tableting has been steadily increas-

FIGURE 1

Direct-compression tableting versus wet and dry granulation



ing in acceptance and use since the 1960s, when the first excipients suitable for DC tableting were developed [2]. Figure 1 shows the manufacturing steps of the different tablet manufacturing processes and enumerates the advantages and disadvantages of DC tableting. The advantages of DC tableting are well known [3]. Since it eliminates several steps in the tablet manufacturing process, DC tableting reduces capital investment, formulation work, and manufacturing costs. Moreover, avoiding the granulation step may help to increase a drug product's stability and improve its dissolution profile.

However, a DC process requires DC excipients, which may present certain disadvantages. For instance, using DC excipients can increase the risk of segregation due to larger differences in particle size distribution between such excipients and many active pharmaceutical ingredients (APIs). In addition, DC excipients are often less compactable than their non-DC versions, so tableting can be more challenging and the product's dilution potential may be reduced [4]. Finally, DC excipients are usually under intellectual property protection of excipient manufacturers, so they can be more expensive and harder to replace.

Since it eliminates several steps in the tablet manufacturing process, DC tableting reduces capital investment, formulation work, and manufacturing costs.

Filler-binders have a considerable impact on the tableting properties of low- and medium-dose tablet formulations. Table 1 lists some examples of currently marketed DC filler-binders along with the composition, manufacturing method, and general properties of each. An optimal DC filler-binder should be free-flowing, inert, and compressible. Additionally, it should have a reproducible, narrow particle size distribution, high dilution potential, and good compactability. Finally, it should also contribute to the tablet's microbiological, chemical, and mechanical stability. Currently marketed DC filler-binders provide most of these key attributes; however, depending on the nature and dose of the API, high dilution potential and good compactability remain challenging.

This article describes a study that used piroxicam to compare the compactability, disintegration, friability, and dissolution profiles of three different DC filler-binders. The study also looked at whether formulators could improve these profiles by adding a dry binder to a DC blend. Finally, the study tested the dry binders' capacity to improve a high-dose tablet formulation of natural calcium carbonate.

Effect of dry binders in medium-dose DC formulations

The study tested three DC filler-binders based on either microcrystalline cellulose (MCC), lactose, or dicalcium phosphate

TABLE 1

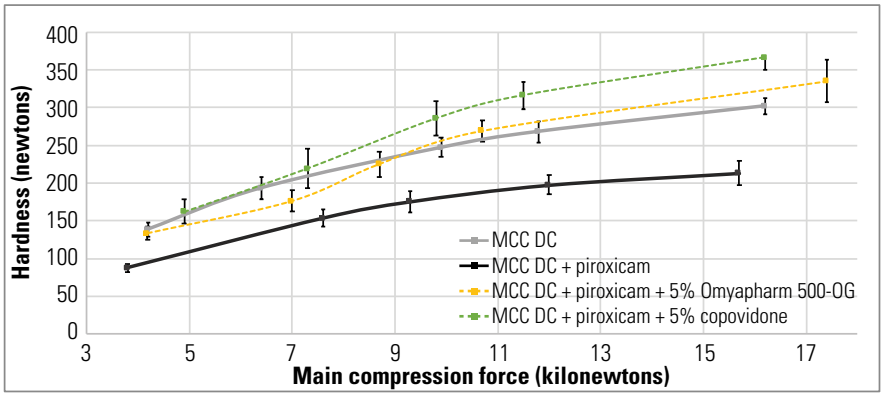
Examples of DC filler-binders

Method	Composition	Ingredient type	Material properties
Spray drying	Lactose monohydrate	Spray-dried lactose	Uniform size, spherical shape, good flow, low compactability, brittle deformation, reducing sugars
Sieving (and/or milling)	Dicalcium phosphate	Dicalcium phosphate anhydrous	Good flow, good compactability, non-hygroscopic, prone to capping, deformation by fragmentation, alkaline residues
Co-drying	Microcrystalline cellulose Colloidal silicon dioxide	Silicified microcrystalline cellulose	Good flow, good compactability, plastic deformation, incompatible with strong oxidizing agents
Spray drying	Lactose Microcrystalline cellulose	Lactose monohydrate, and microcrystalline cellulose	Superior flow and binding properties, plastic-brittle deformation, reducing sugars, incompatible with strong oxidizing agents
Spray drying	Lactose monohydrate Starch	Lactose monohydrate and corn starch	Good compactability, good flow, good disintegration, elastic-brittle deformation, reducing sugars, hygroscopic

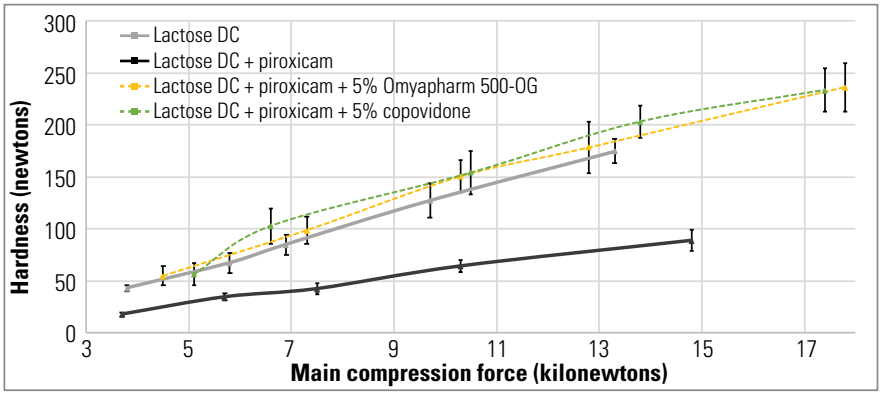
Figure 2

Compactability of DC formulations containing 10% piroxicam with and without dry binders

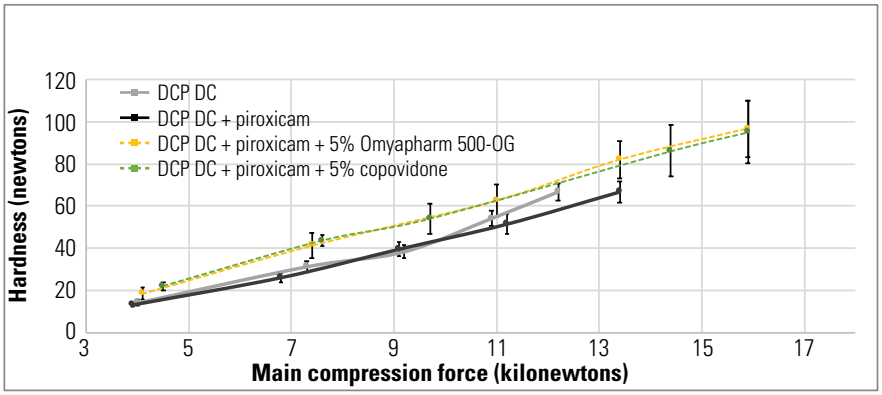
a. MCC-based formulations



b. Lactose-based formulations



c. DCP-based formulations



(DCP). The tableting blends contained magnesium stearate as lubricant and croscarmellose sodium as superdisintegrant. The dry binders used were a well-known commercially available brand of copovidone and Omyapharm 500-OG, a large-surface-area, porous mineral excipient [5, 6]. The ingredients were mixed in a WAB Turbula T10F mixer, and both placebo and 10 percent piroxicam-containing tablets of 200 milligrams were manufactured at 15,000 tablets per hour in a Fette 1200i rotary tablet press. Hardness, friability, disintegration time, and dissolution were measured according to *Eur. Pb.* using a Pharmatron MultiTest 50, an Erweka TAR 102, a Pharmatron DisiTest 50, and a Sotax AT7smart.

Compactability. As shown in Figures 2a and 2b, adding only piroxicam to the MCC- and lactose-based filler-binders negatively impacted compactability. For the MCC-based filler-binder, the piroxicam reduced tablet hardness by about 50 newtons through the entire compression range tested. For the lactose-based filler-binder, the piroxicam reduced tablet hardness up to 50 newtons at lower compression forces and 75 newtons at higher compression forces. Adding piroxicam did not affect compactability for the DCP-based filler-binder (Figure 2c), although the tablets achieved a hardness of only 50 newtons at more than 10 kilonewtons of compression force, indicating that the compactability of the filler-binder alone is very low.

Adding 5 percent dry binder to either the MCC- or lactose-based formulations restored their compactability to the placebo level (Figures 2a and 2b). Moreover, at high compression forces copovidone significantly improved the compactability of a 10 percent piroxicam MCC-based formulation. For the DCP-based formulation, adding dry binders only marginally improved compactability (Figure 2c).

Friability. Figure 3b shows that adding piroxicam did not affect friability for lactose-based tablets, although friability was higher than 0.5 percent for compression forces below 9 kilonewtons. Conversely, piroxicam severely impacted friability for MCC-based tablets, as shown in Figure 3a. While friability was below 0.03 percent for the whole compression force range tested (4 to 16 kilonewtons) for placebo tablets, when piroxicam was added to the formulation, the MCC-based tablets exhibited a severe dependence on compression force, reaching 2.3 percent for 88-newton tablets and 0.75 percent for 128-newton tablets. Although the addition of piroxicam did not generally affect the friability of DCP-based tablets, no mechanically stable piroxicam tablets with compression forces below 7 kilonewtons could be manufactured (Figure 3c).

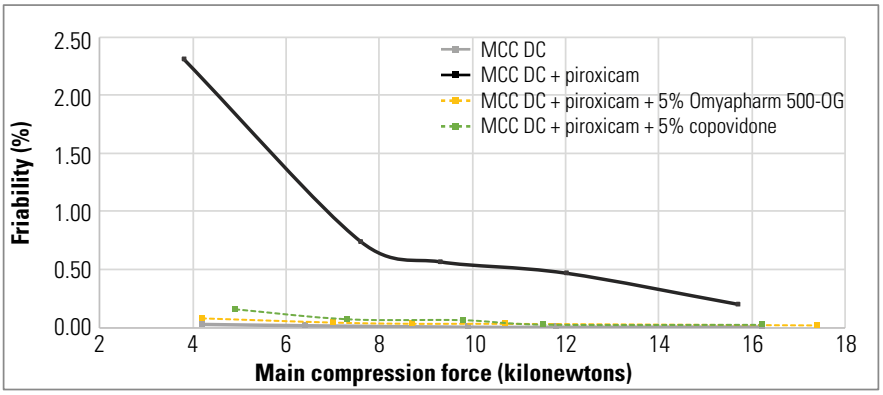
Interestingly, both dry binders also increased the mechanical stability of lactose-based tablets, allowing for friability lower than 0.2 percent for 50-newton tablets.

Both copovidone and Omyapharm 500-OG at a 5 percent level, restored the friability of the MCC-based formulation to placebo levels (Figure 3a). Interestingly, both dry binders also increased the mechanical stability of lactose-based tablets, allowing for friability lower than 0.2 percent for 50-newton tablets (Figure 3b). On the contrary, adding the dry binders to the DCP-based formulation had no impact on friability (Figure 3c).

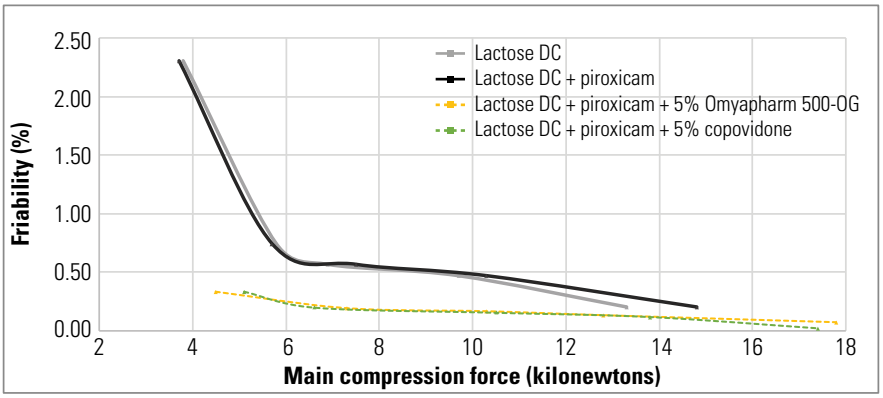
Figure 3

Friability of DC formulations containing 10% piroxicam with and without dry binders

a. MCC-based formulations



b. Lactose-based formulations



c. DCP-based formulations

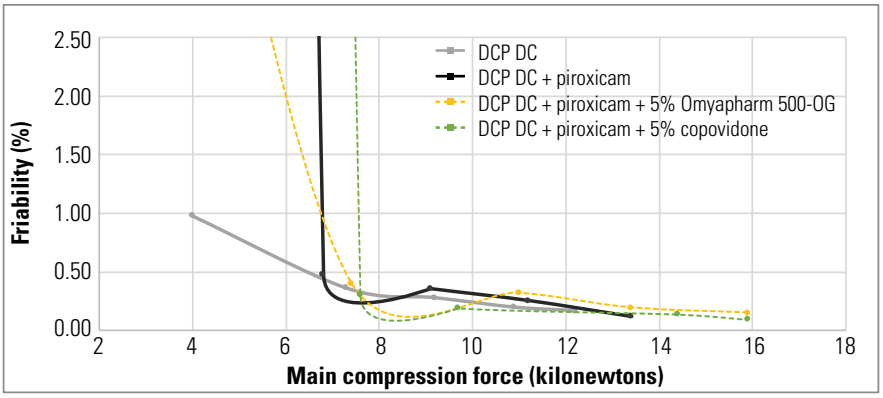
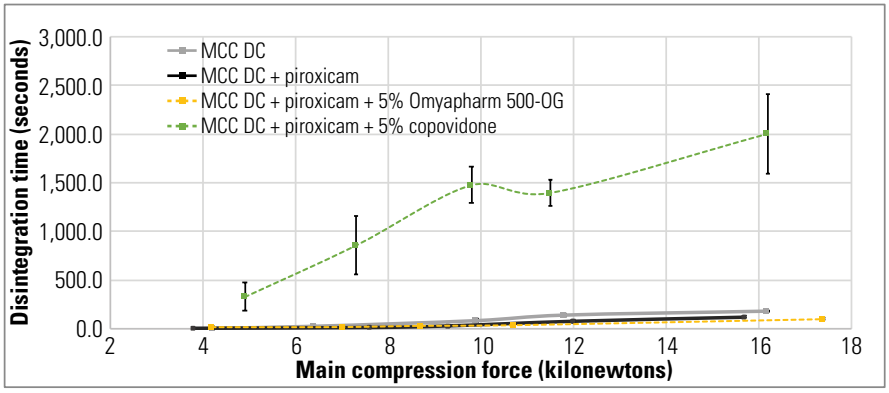


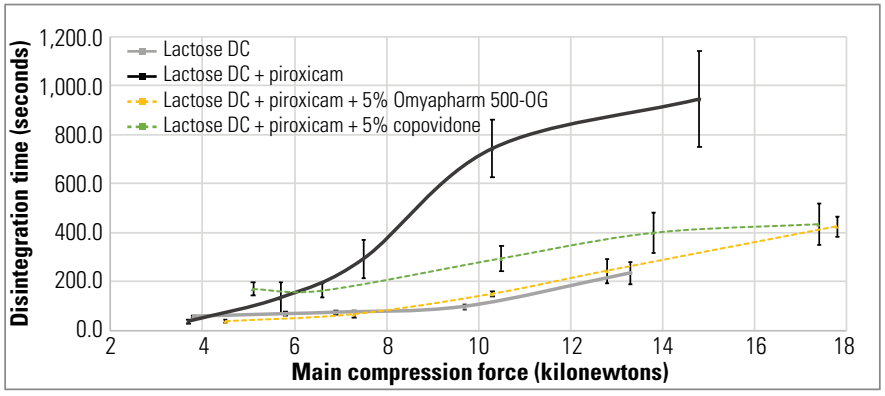
Figure 4

Disintegration time of DC formulations containing 10% piroxicam with and without dry binders

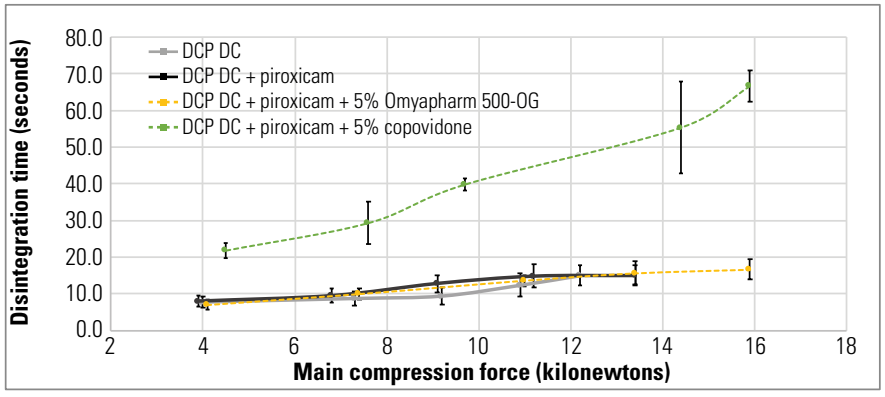
a. MCC-based formulations



b. Lactose-based formulations



c. DCP-based formulations



Disintegration time. Piroxicam did not affect the disintegration time of the DCP-based formulation, whereas it decreased that of MCC-based tablets and increased that of lactose-based tablets. Figure 4b shows how the disintegration time of the piroxicam-containing lactose-based formulation is highly dependent on hardness, resulting in a disintegration time 6.5 times that of the lactose-based placebo at the same compression force. For example, 10 kilonewtons of compression force resulted in lactose-based placebo tablets with a hardness of 128 newtons and a disintegration time of less than two minutes, while the same compression force resulted in piroxicam-containing tablets with hardness of 64 newtons and a disintegration time of approximately 12 minutes.

Adding piroxicam to the MCC-based formulation reduced the disintegration time up to 40 percent. Omyapharm 500-OG did not affect this reduction, while copovidone increased it significantly (Figure 4a). Not only did the disintegration time increase with the addition of copovidone, but disintegration also became strongly dependent on tablet hardness. Nevertheless, tablets with high hardness and acceptable friability could be manufactured with disintegration times of less than 5 minutes. Both dry binders significantly decreased the disintegration time of the lactose-based piroxicam-containing tablets, but only Omyapharm 500-OG restored it to the level of the lactose-based placebo tablets. Omyapharm 500-OG did not affect the disintegration time of the DCP-based formulation, whereas copovidone increased disintegration time significantly. However, even for the DCP-based formulation with copovidone, disintegration times remained very fast—less than 75 seconds—for the entire compression force range tested.

Drug dissolution. Figure 5 shows the dissolution profiles of piroxicam formulated with one of

the three DC filler-binders, with and without the dry binders. Eighty percent of piroxicam was dissolved in less than 15 minutes for all formulations. Omyapharm 500-OG accelerated the dissolution for all three filler-binder formulations, while copovidone accelerated only that of the MCC-based formulation and delayed that of the DCP and lactose-based formulations.

These results clearly indicate that even a small amount of API can have negative effects on the final dosage form's properties. A decrease in compactability leads to the use of higher compression forces to achieve mechanically stable tablets. In turn, high compression forces increase the risk of capping and cause strain on the tableting equipment. Additionally, the temperature of the tooling may increase, reducing the formulation's chemical stability. Negative effects on friability lead to tablets that are not mechanically stable, making them unsuitable for coating, if required, or transportation, unless special packaging is used, which may dramatically increase costs. Disintegration time and dissolution may also be affected, which can be problematic in products where these properties are considered critical.

These results clearly indicate that even a small amount of API can have negative effects on the final dosage form's properties.

Effect of dry binders in a high-dose DC formulation

The piroxicam study showed that adding small amounts of dry binders to medium-dose MCC-, lactose-, or DCP-based DC formulations could improve tabletability. To determine the effects of dry binders in high-dose tablets, researchers blended directly compressible natural calcium carbonate (NCC DC) with the lubricant magnesium stearate and the superdisintegrant croscarmellose sodium. As in the piroxicam study, the researchers used the dry binders copovidone and Omyapharm 500-OG. The ingredients were mixed in a WAB Turbula T10F mixer and compressed into 200-milligram tablets containing either 90 percent NCC and no dry binder or 85 percent NCC and 5 percent dry binder. Again, the tablets were manufactured at 15,000 tablets per hour in a Fette 1200i rotary tablet press. The tablets were then measured for hardness, friability, disintegration time, and dissolution according to *Ph. Eur.* using a Pharmatron MultiTest 50, an Erweka TAR 102, Pharmatron DisiTest 50, and a Sotax AT7smart.

Compactability, friability, and disintegration time. Figure 6a shows how the addition of both dry binders significantly improved the compactability of NCC DC and allowed the use of higher compression forces without capping. Also, adding 5 percent copovidone or Omyapharm 500-OG decreased tablet friability considerably, resulting in mechanically stable tablets at much lower compression forces. Finally, the NCC DC tablets disintegrated rather quickly, independent of tablet hardness. Adding Omyapharm 500-OG, significantly reduced the disintegration time, particularly at lower compression forces. Copovidone increased to more than double the disintegration time along the entire range of compression forces tested.

Study summary

Table 2 summarizes the advantages of using dry binders to improve DC formulations containing either 10 percent piroxicam or 90 percent NCC. As shown in the table, both copovidone and Omyapharm 500-OG can improve the tableting process and tablet properties. However, the choice of the appropriate filler-binder and dry binder combination will depend on the intended properties of the final

FIGURE 5

API dissolution rate of DC formulations containing 10% piroxicam with and without dry binders (Error bars represent the standard deviation of 6 tablets of equal hardness.)

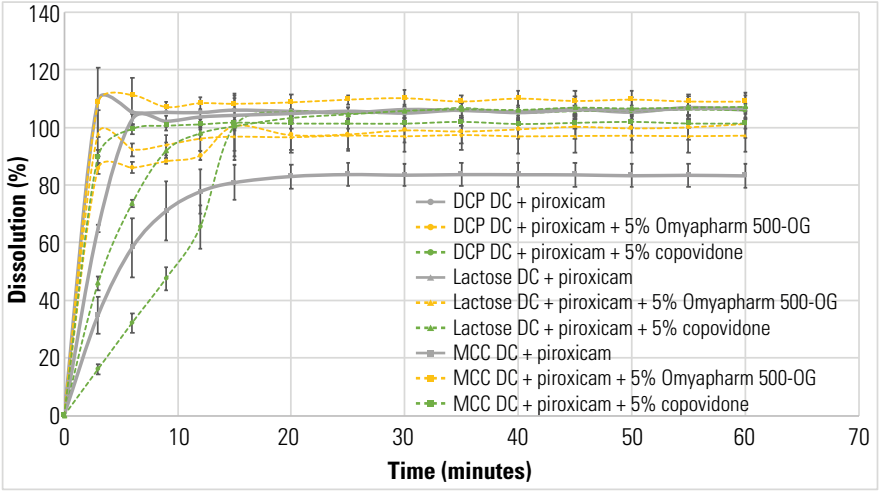
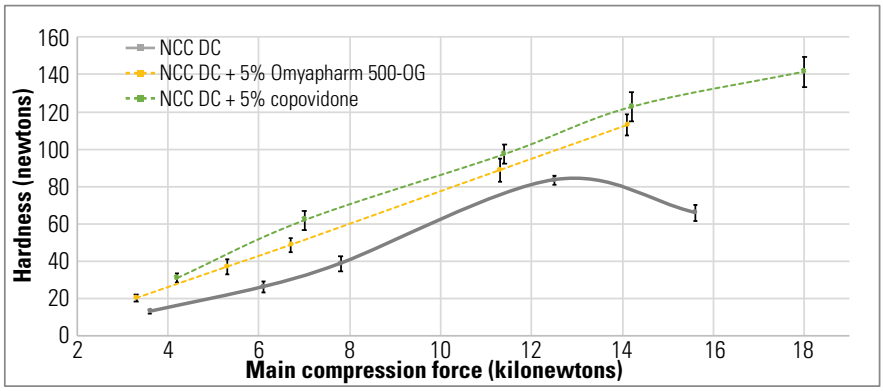


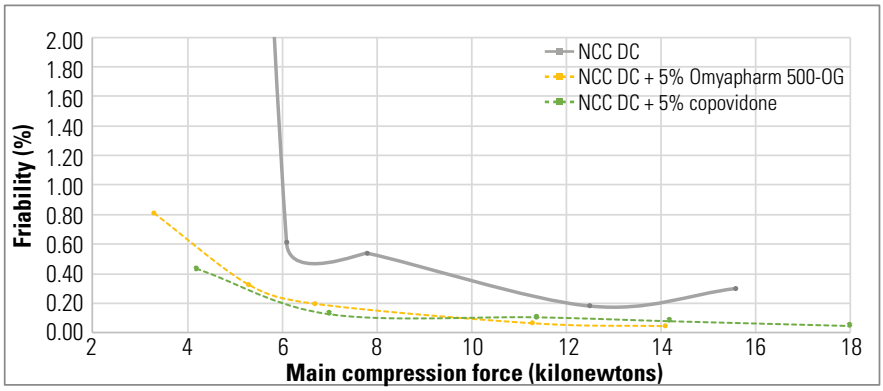
Figure 6

Effect of adding dry binders to 90% NCC DC formulation (85% NCC + 5% dry binder after addition)

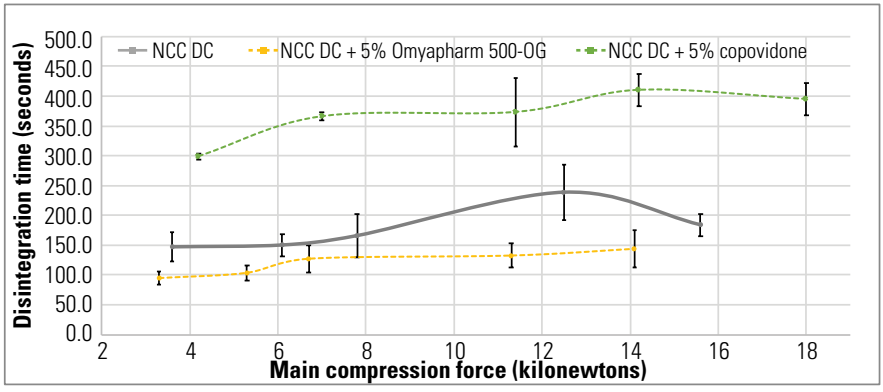
a. Hardness versus compression force



b. Friability versus compression force



c. Disintegration time versus compression force



dosage form as well as the dose and inherent properties of the API.

The choice of the appropriate filler-binder and dry binder combination will depend on the intended properties of the final dosage form as well as the dose and inherent properties of the API.

For example, it seems possible that the tested dry binders cannot sufficiently improve DCP-based DC formulations to justify their addition. For MCC-based DC formulations, although both binders could significantly improve compactability, friability, and dissolution, they might not bring a benefit in terms of disintegration time. For lactose-based DC formulations, adding the dry binders may improve compactability, friability, and disintegration time but might have no effect on dissolution. For high-dose NCC DC formulations, while adding the tested dry binders may yield significant benefits in compactability and friability, disintegration time will depend on the binder used. Generally, Omyapharm 500-OG improved disintegration time more than copovidone, which could become relevant for companies developing fast-disintegrating tablets.

Another variable to consider when selecting which dry binder to use could be its potential incompatibility with the API. While Omyapharm 500-OG might provide a hostile environment to alkaline-sensitive APIs, copovidone might contain per-

oxides that could degrade peroxide-sensitive APIs. More data with different APIs and doses are necessary to be able to make valid general predictions; however, this study provides useful insight into the types of benefits each dry binder brings to either high-dose or medium-dose API-containing DC formulations. *T&C*

References

1. A. G. Mirani, et al., "Direct compression high functionality excipient using coprocessing technique: A brief review," *Current Drug Delivery*, 2011, Vol. 8, No. 4, pages 426-435.

2. Gregory Thoorens, et al., "Microcrystalline cellulose, a direct compression binder in a quality by design environment—A review," *International Journal of Pharmaceutics*, 2014, Vol. 473, No. 1-2, pages 64-72.

3. Zhe Li, et al., "Composite particles based on particle engineering for direct compaction," *International Journal of Pharmaceutics*, 2017, Vol. 519, No. 1-2, pages 272-286.

4. John Rojas, "Excipient design by co-processing for direct compression applications," In: Ajit S. Narang, H.S. Boddu (eds.) *Excipient Applications in Formulation Design and Drug Delivery*, Springer, 2015.

5. Carolina Diaz Quijano, "Eye on Excipients: Functionalized calcium carbonate," *Tablets & Capsules*, September 2015, pages 44-48.

6. Carolina Diaz Quijano, "Directly compressible ODT platforms: a comparison study," Tablets & Capsules, July 2018, pages 18-23.

TABLE 2

Summary of the effects of adding dry binders to 10% piroxicam and 90% NCC DC formulations (85% NCC after addition of 5% dry binder)

		Compactability	Friability	Disintegration time	Dissolution
DCP DC + 10% piroxicam	Omyapharm	+	0	0	0
	Copovidone	+	0	-	--
MCC DC + 10% piroxicam	Omyapharm	++	++	0	++
	Copovidone	++	++	--	++
Lactose DC + 10% piroxicam	Omyapharm	++	++	++	0
	Copovidone	++	++	++	--
85% NCC DC	Omyapharm	++	++	+	Not measured
	Copovidone	++	++	--	

Key
0 no effect
- marginally negative
-- significantly negative
+ marginally positive
++ significantly positive

Carolina Diaz Quijano (+41 62 789 2274, carolina.diazquijano@omya.com) is head of technical services for consumer goods and Javier Camargo is global business development manager at Omya International (www.omya.com).