An Executive Summary

Comprehensive Analysis into Disintegration Mechanisms: How Reliable are Textbook Recommendations?

Emily Sabath
Scientist, Research & Development
JRS Pharma

Introduction

When formulating a tablet, the solubility of the tablet matrix is often used as the sole criterion for disintegrant selection. Most formulators tend to select swelling-type disintegrants for insoluble matrices and wicking-type disintegrants for soluble matrices.

This article provides an overview to disintegration and disintegration mechanisms, as well as an in-depth analysis of the effects of superdisintegrants as related to tablet hydrophobicity and storage. In addition, the effect of high-humidity environments on tablet surfaces containing different superdisintegrants is examined. Textbook recommendations and assumptions versus actual data from studies of disintegrants in hydrophobic insoluble tablet matrices will be presented.

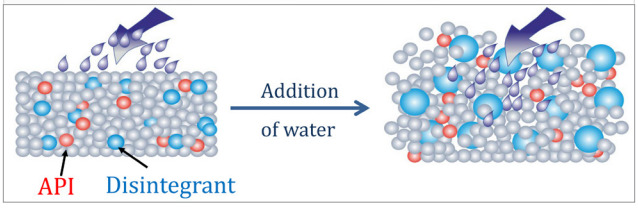
Overview: Disintegrants

In the context of pharmaceuticals, disintegration refers to tablets or capsules breaking up in an aqueous environment. The environment in which the disintegration is intended to occur (e.g., a beverage, saliva, gastric fluid, intestinal or colonic fluid) varies depending on the API's mode of action and how it is administered.

Why is disintegration important? Rapid disintegration is the key for drug bioavailability. Once the tablet is broken apart, the available surface area multiplies. The increase in surface area allows the API to have more exposure to the disintegration media, thus promoting a more rapid release of API and possibly more efficient therapy for the patient.

There are three mechanisms of disintegration: swelling, wicking, and shape recovery. The three most commonly used disintegrants in the industry today—sodium starch glycolate (SSG), croscarmellose sodium (CCS) and crospovidone (cPVP)—are good examples of how these mechanisms work in the context of pharmaceutical dosage forms.

Figure 1: Swelling mechanism of disintegration.

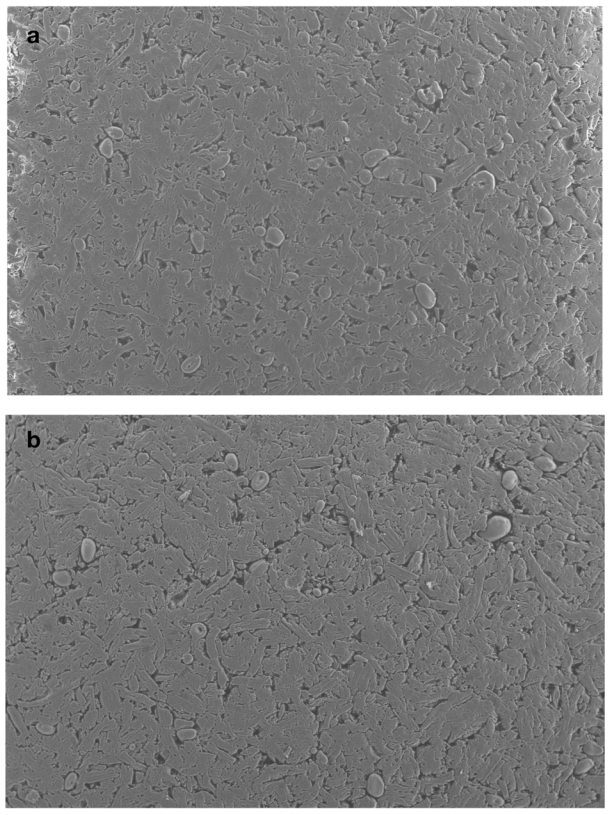


Swelling-type disintegrant: SSG. SSG is a cross-linked carboxymethylated potato starch that has good flow and is allergen free (e.g., EXPLOTAB® and VIVASTAR® from JRS). Cross-linking is a chemical process that bonds or links one polymer chain to another. As a disintegrant, SSG operates through a swelling mechanism, which is illustrated in **Figure 1**. When a matrix tablet comprising an API (shown in red) and disintegrant (shown in blue) comes in contact with water, the disintegrant particles swell, causing the tablet to break apart and release the API. Swelling-type superdisintegrants

SPONSORED BY

JRS PHARMA The Global Excipient Maker
JRS FAMILY A Member of the JRS Group

Figure 2: Scanning electron microscope images (100x) of the surface of a tablet containing 95% microcrystalline cellulose (MCC), 4% sodium starch glycolate (SSG), and 1% sodium stearyl fumarate (SSF). (a) Tablet surface immediately after compaction. (b) Same tablet surface after 2 days exposure to high temperature and humidity.



like SSG are most effective with insoluble tablet matrices because the swelling disintegrant particles require resistance in the tablet to develop their full disintegration force.

A scanning electron microscope (SEM) image of the surface of a tablet containing 95% microcrystalline cellulose (MCC), 4% SSG, and 1% sodium stearyl fumarate (SSF) is shown in **Figure 2**. In **Figure 2a**, the round individual SSG particles are visible throughout the tablet surface immediately after compression. Then, the tablet was subjected to high temperature, high humidity environment (40 degrees C, 70% relative humidity). After two days in these conditions, the tablet surface was examined under SEM again (**Figure 2b**). In this image, one can see that the SSG particles have started to absorb moisture from the humid environment and to swell.

Wicking disintegrant: CCS. Derived from either cotton or wood, CCS is cross-linked sodium carboxymethyl cellulose (e.g., VIVASOL® from JRS) and is an example of

Figure 3: Wicking mechanism of disintegration.

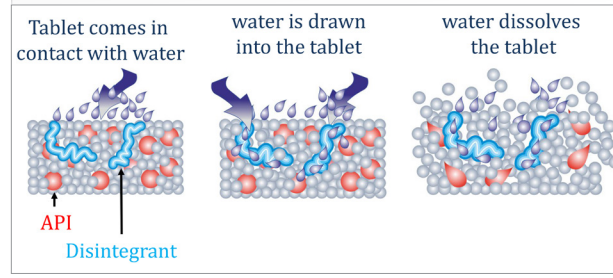
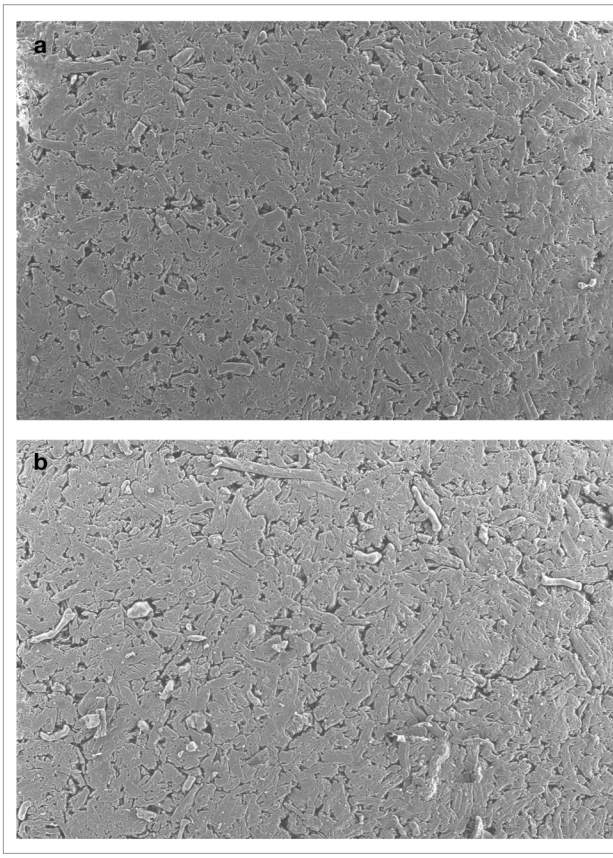


Figure 4: Scanning electron microscope images (100x) of the surface of a tablet containing 95% microcrystalline cellulose (MCC), 4% croscarmellose sodium (CCS), and 1% sodium stearyl fumarate (SSF). (a) Tablet surface immediately after compaction. (b) Same tablet surface after 1 day exposure to high temperature and humidity.



a wicking-type disintegrant. With the wicking mechanism (a.k.a. capillary action), fluid is drawn into the tablet and dissolves the tablet matrix rapidly. **Figure 3** shows the wicking disintegration mechanism illustrated as fibrous CCS particles in blue and API in red. The disintegration material draws water into the tablet and dissolves it from within.

Figure 4a shows SEM images of tablet surfaces that contain 95% MCC, 4% CCS, and 1% SSF after

Figure 5: Superdisintegrants in storage: croscarmellose sodium (CCS tablets).

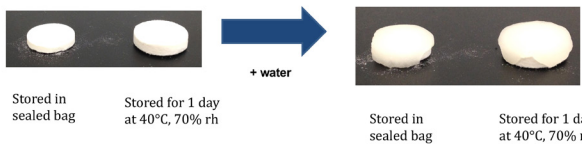


Figure 6: Shape recovery mechanism of disintegration.

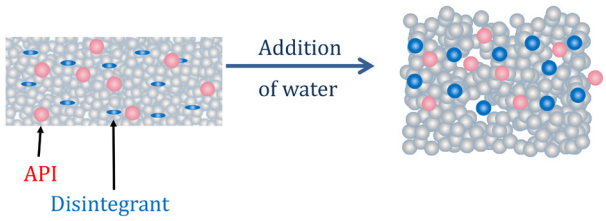


Figure 7: Scanning electron microscope (SEM) images (100x) of the surface of a tablets containing 95% microcrystalline cellulose (MCC), 4% crospovidone (cPVP), and 1% sodium stearyl fumarate (SSF). (a) Tablet surface immediately after compaction. (b) Same tablet surface after 1 day exposure to high temperature and humidity.

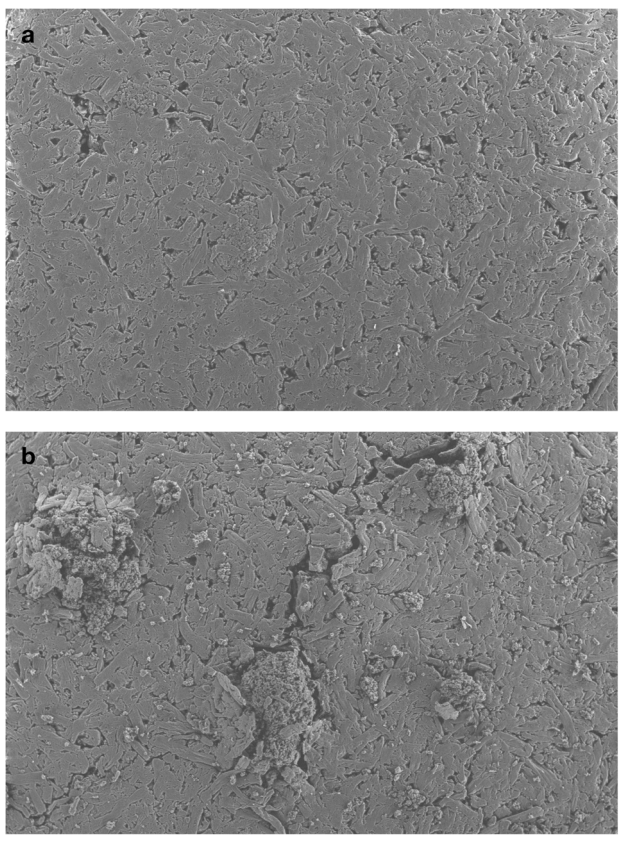
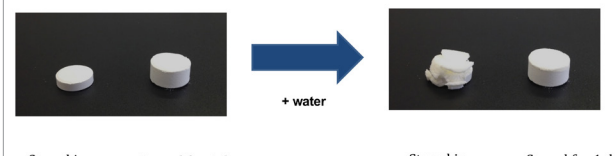


Figure 8: Superdisintegrants in storage: crospovidone (cPVP) tablets.



compaction. The small fibrous CCS particles are hard to distinguish from the fibrous MCC material. **Figure 4b** shows the same tablet surface after one day in a high humidity, high temperature environment (40 degrees C, 70% relative humidity). Here, you can differentiate the CCS particles from the MCC because they have started to swell from the humid environment.

Figure 5 shows two tablets made with 100% CCS: the tablet on the left was stored in a sealed aluminum bag and the one on the right was stored on the benchtop. Both tablets were kept at 40 degrees C, 70% relative humidity. The tablet that is left open on the benchtop (right) has started wicking moisture from the humid environment and started to expand. When additional water was added to these tablets, both started to disintegrat.

Multi-acting disintegrant: cPVP. cPVP is a cross-linked polyvinyl pyrrolidone (e.g., VIVAPHARM® PVPP XL from JRS) and has several important attributes: excellent compressibility, non-ionic (resulting in pH independent disintegration), and allergen free.

cPVP operates through a series of disintegration mechanisms: swelling, wicking, and shape recovery. With shape recovery, disintegrant particles, which have been compressed during tablet compaction, bounce back to their original shape when in contact with moisture. The stored potential energy in the compressed disintegrant becomes kinetic energy as it expands with the addition of water, causing the tablet to break apart (see **Figure 6**).

Figure 7 shows SEM images of tablet surfaces containing 95% MCC, 4% cPVP, and 1% SSF. **Figure 7a** shows the tablet surface right after compaction. Upon close examination of the SEM, a few cPVP particles are visible on the tablet surface. **Figure 7b** shows the tablet after one day in storage in a high temperature, high humidity environment. The cPVP has pulled in moisture from the humid environment and has started to affect the tablet surface, which is cracked due to the shape recovery of the cPVP itself.

Figure 8 shows tablets made with 100% cPVP and no other excipients. They were stored in a high humidity, high temperature environment (40 degrees C, 70% relative humidity), with the left tablet stored in a sealed aluminum bag and the right stored on the benchtop. The tablet

Figure 9: Comparison of settling volumes among three superdisintegrants: crospovidone (cPVP), sodium starch glycolate (SSG), and croscarmellose sodium (CCS).

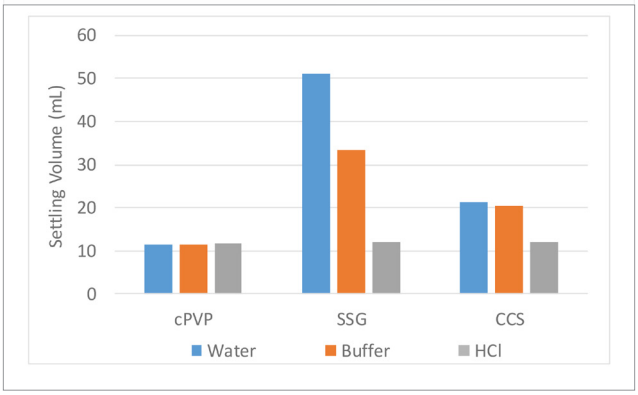
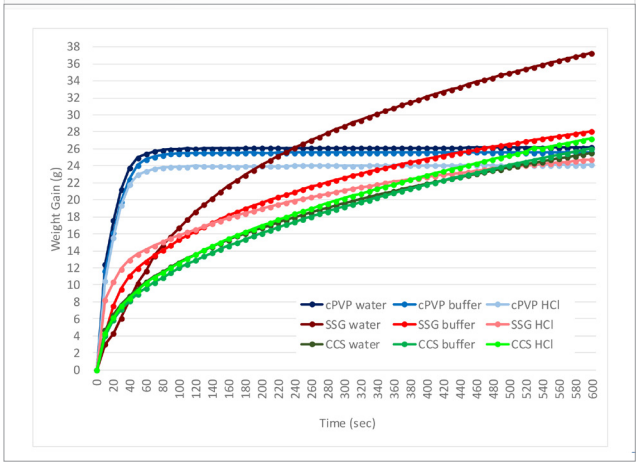


Figure 10: Comparison of liquid uptake among disintegrants.



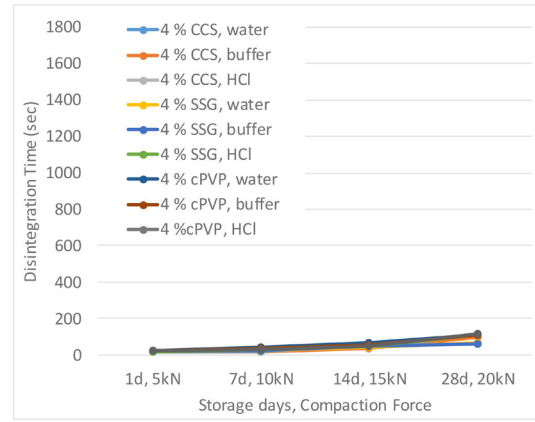
on the right has started to expand (shape recovery) by pulling moisture in from the humid outside environment. When you add a few drops of water to these tablets, the left tablet, which was stored in the sealed bag, begins to disintegrate; the one on the right does not.

Challenging Textbook Recommendations for Disintegrants

Textbook recommendations generally suggest using wicking disintegrants for soluble matrices, swelling disintegrants for insoluble matrices, and shape recovery universally. Swelling disintegrants are used with insoluble matrices as they require resistance to break tablets apart. CCS and SSG carry carboxyl groups and are therefore expected to exhibit pH dependence, however cPVP is pH independent.

JRS completed a study comparing settling volumes as a measure for the swelling component of the disintegrants' action. **Figure 9** compares the settling volumes of the three disintegrants in water, a pH 6.8 phosphate buffer, and a 0.1N HCl acid solution. While cPVP exhibited low and pH-independent swelling, SSG showed the highest degree of swelling in water, but was strongly affected by ionic strength and pH. CCS took an intermediate position between cPVP and SSG in this study in terms of swelling and susceptibility to pH.

Figure 11: Data summary: Microcrystalline cellulose (MCC) and dibasic calcium phosphates (DCP) tablets containing 10% LUBRITAB® (hydrophobic model compound) and 4% superdisintegrant.



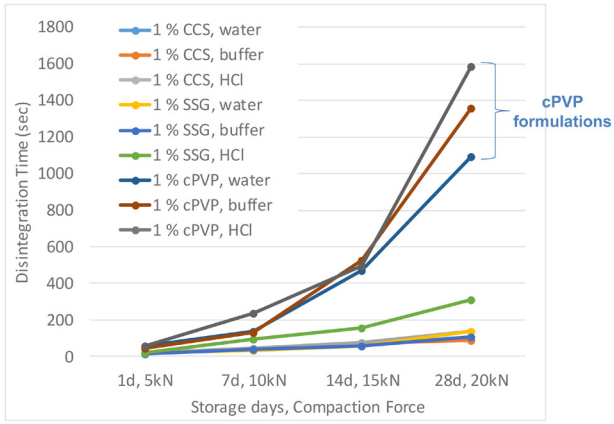
In order to quantify the wicking component of the disintegrants' action, liquid uptake rates into powder beds of the disintegrants were measured. The results of this test are shown in **Figure 10** where the time in seconds is represented on the X-axis, and the weight gain in grams on the Y-axis. The findings indicated that CCS (green) has a sustained liquid uptake, which is pH independent. SSG (red) also has a sustained liquid uptake but increased with water, showing the pH dependency. cPVP (blue) had a fast liquid uptake and was pH independent.

The next series of studies examined disintegrant selection and were designed to test textbook recommendations with insoluble hydrophobic matrix tablets.

This study design used a tablet matrix consisting of 17% or 20% VIVAPUR® MCC, 68% EMCOMPRESS® DCP (dibasic calcium phosphates), 10% LUBRITAB® hydrogenated vegetable oil (hydrophobic model compound), each of the three disintegrants (SSG, CCS, and cPVP) at 4% or 1%, respectively, and 1% PRUV® SSF as lubricant. The study examined disintegration of this tablet matrix in water, pH 6.8 phosphate buffer, and 0.1N HCl. It also examined storage times at 1, 7, 14, and 28 days in a high-temperature environment in sealed aluminum bags.

Figure 11 shows the cross-sectional data of the tablets disintegrating in the various medias over various storage times for tablets containing 4% disintegrant. The graph indicates that all tablets containing 4% disintegrant

Figure 12: Data summary: Microcrystalline cellulose (MCC) and dibasic calcium phosphates (DCP) tablets containing 10% LUBRITAB® (hydrophobic model compound) and 1% superdisintegrant.



disintegrated in all medias in less than 200 seconds. Note that the placebo tablets (not graphed) with 0% disintegrant took quite often more than 1 hour for complete disintegration to occur.

Conducting the same test, except using 1% disintegrant instead of 4%, the results were quite different. **Figure 12** shows the cross-sectional data of the tablets disintegrating in the various medias over various storage times with only 1% disintegrant. Notice that several of the tablets and conditions are still conducive of less than 200 seconds disintegration including all of the tablets containing CCS. However, what is interesting are those scenarios that have increased disintegration time, namely all the cPVP formulations as well as the 1% SSG in HCl media.

The tablets containing 1% SSG in the 0.1N HCl solution show increasing disintegration times for increased storage days and compression forces. However, the tablets containing the 1% SSG in water or phosphate buffer are still under 200 seconds disintegration. This illustrates the pH dependence of SSG as expected based on the textbook recommendations.

Of all the tablets containing cPVP, only the tablets at the lower compaction forces (5-10 kN) and lower storage days (1-7 days) disintegrate in less than approximately 200 seconds. As you increase compaction force greater than 10 kN and storage days of 14 days or greater, the tablets take increasingly longer to disintegrate up to approximately 1600 seconds (~27 minutes). The tablets containing the cPVP in the 0.1N HCl solution have the longest disintegration times illustrating an unexpected pH dependence.

The results of these studies clearly showed some discrepancy between textbook assumptions and actual study findings.

Figure 13: Disintegration times (hours: minutes: seconds) in an insoluble hydrophobic tablet containing 0% or 0.25% disintegrant as indicated.

				combo	swelling	wicking	
	MCC	DCP	no disintegrant	PVPP XL	SSG	CCS	Emcosoy
1.37 MPa	100%	0%	0:01:12	0:01:57	0:01:00	0:01:08	0:01:48
	75%	25%	0:03:45	0:02:35	0:01:00	0:00:58	0:02:03
	50%	50%	0:05:55	0:03:42	0:01:59	0:01:40	0:02:48
	25%	75%	0:46:36	0:08:26	0:02:00	0:02:43	0:10:18
	0%	100%	16:39:00+	16:39:00+	16:39:00+	16:39:00+	16:39:00+
2.66 MPa	MCC	DCP	no disintegrant	PVPP XL	SSG	CCS	Emcosoy
	100%	0%	0:11:41	0:08:19	0:02:38	0:02:38	0:07:39
	75%	25%	0:15:39	0:09:34	0:04:32	0:02:55	0:07:56
	50%	50%	0:17:40	0:07:22	0:07:21	0:03:19	0:09:56
	25%	75%	1:35:16	0:22:25	0:19:15	0:04:49	0:32:39
	0%	100%	16:39:00+	16:39:00+	16:39:00+	16:39:00+	16:39:00+
3.02 MPa	MCC	DCP	no disintegrant	PVPP XL	SSG	CCS	Emcosoy
	100%	0%	0:18:01	0:14:26	0:03:07	0:03:47	0:08:52
	75%	25%	0:22:29	0:12:07	0:06:46	0:05:08	0:11:05
	50%	50%	0:24:21	0:11:11	0:06:50	0:06:09	0:24:48
	25%	75%	16:39:00+	0:56:05	0:25:50	0:05:35	3:43:28
	0%	100%	16:39:00+	16:39:00+	16:39:00+	16:39:00+	16:39:00+

0 - 5minutes
5 - 10minutes
10 - 20minutes
20 - 30minutes
30 min - 2hrs
2 hours +

- According to theory, SSG should work best in insoluble formulations followed by cPVP and CCS. The study results indicated that CCS showed the best overall performance, followed by SSG and cPVP.
- SSG and CCS were expected to lose efficiency in acidic medium (HCl), but testing showed that this effect was only observed for the low concentration (1%) SSG at higher compaction forces and longer storage duration. CCS performance was pH independent.
- cPVP was expected to perform better than CCS, regardless of the media's pH, but it was shown that at 1% concentration, cPVP was the least efficient disintegrant tested in all media. Additionally, cPVP tablets showed pH dependency whereas the media got more acidic, the disintegration time increased.

Another study further testing textbook recommendations had the objective of determining the efficiency of various disintegrants in a different insoluble hydrophobic tablet matrix. These formulations contained EMCOCEL® MCC and EMCOMPRESS® DCP binder/filler titrated in ratios of 100:0, 75:25, 50:50, 25:75 or 0:100 MCC:DCP. In addition to binder/filler, disintegrant was added as 0% for the placebo tablets or 0.25%. Superdisintegrants included VIVAPHARM® PVPP XL, EXPLOTAB® SSG, VIVASOL® CCS, or EMCOSOY® (soy fiber polysaccharide). LUBRITAB® hydrogenated vegetable oil was added as the hydrophobic model compound at 10% of the total formulation. The binder/filler, disintegrant, and hydrophobic model compound were blended for 15 minutes, followed by the addition of PRUV® SSF as lubricant and blended for an additional 5 minutes, and then the mixture was pressed into tablets using a rotary tablet press.

An overview of the results can be seen in **Figure 13**. The results are grouped by tablet tensile strength (far-left column), various ratios of binder/filler (columns 2 and 3), which is ~89% of the total tablet formulation, and disintegrant type (columns 4-8).

Three general trends are observed immediately from the data summary table. As tablet tensile strength increases, disintegration time tends to increase. As you increase the concentration of DCP in the tablet, the disintegration time increases. Also not surprising, the placebo tablets that contain 0% disintegrant generally take longer to disintegrate.

Taking a closer look at the data, at the lowest tensile strength, 1.37 MPa, most of the tablets disintegrated quickly. When increasing tensile strength to 2.66 MPa, however, SSG was surprisingly not the best performer; CCS disintegrated tablets the fastest across all formulations presented. Increasing tensile strength again to 3.02 MPa, SSG and CCS demonstrated almost equivalent disintegration efficiency except at the 25% MCC 75% DCP tablets where the CCS tablets disintegrated approximately 5x faster than the tablets containing SSG. At 100% DCP, at all tensile strengths tested, there was no disintegration, which is believed to be due to the very low porosity of the corresponding tablets. It was concluded that CCS performed best in formulations with higher tensile strength and DCP concentration. This was due to the lack of water ingress into the tablet in case of the less wicking disintegrants.

Soy polysaccharides and cPVP performed almost the same at the low and mid-tensile strength. As noted previously, cPVP works via a combination of disintegration mechanisms (swelling, wicking and shape recovery), but both materials, cPVP and the soy polysaccharides, appear to be primarily using their wicking potential to aid in the disintegration of these tablets. Additionally, this shows that the soy polysaccharides are not as efficient a wicking disintegrant in this matrix as CCS.

Another conclusion from this study is that, in addition to matrix solubility, porosity and hydrophobicity are important factors for disintegrant selection, as they influence the ability of the tablet to get wet and to activate the disintegration power. With LUBRITAB®, a model for hydrophobic APIs, the strong wicking of CCS was found to be the most effective. Swelling of SSG was not effective with high tensile strength tablets due to insufficient contact with water, and cPVP was less effective than SSG or CCS for all tablets tested.

Conclusion

For insoluble hydrophobic matrices, the strong wicking action of CCS was found to be the most relevant mechanism to overcome the tablet's hydrophobicity. The strong swelling of SSG was not effective in these hydrophobic tablets due to the lack of water ingress. The short-term action of cPVP was insufficient at lower concentrations to break up the hydrophobic, plastically deforming matrix.

In addition, the studies concluded that solubility of the tablet matrix is not the only factor to consider when choosing a disintegrant. Tablet deformation characteristics, porosity, tensile strength, and the overall hydrophobicity are significant contributing factors. All disintegrants are hydrophilic and if the storage environment is challenging, the necessary controls and appropriate disintegrant must be selected. Also, pH effects of tablet disintegrants is a consideration depending on where the tablet is targeted to disintegrate in the body.