UNLOCK THE POTENTIAL OF MOISTURE SENSITIVE INGREDIENTS

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Introduction

Active pharmaceutical ingredients (APIs) are mixed with excipients to form a final formulation, which imparts the required therapeutic action. The use of excipients for the formulation of therapeutic actives is inevitable. Including excipients thus creates a high possibility of APIs undergoing certain physical and chemical changes. Any API or excipient will be exposed to a certain degree of moisture during its shelf life. There are many APIs that exhibit undesirable changes both physically and chemically when exposed to moisture. Thus, this exposure to moisture may have a deleterious impact on patient compliance and safety.

The possibility of changes in the physicochemical properties of APIs when exposed to moisture is attributed to a few functional groups that have the highest tendency to hydrolysis. These groups could be acetals, ketals, hemiacetals, hemiketals, imines, alkyl halides, phosphate esters, and sulfate esters. There are various ways to protect the APIs from hydrolysis such as (1) packaging, (2) moisture protection in dosage forms – moisture protective coatings, (3) process – use of process which avoids moisture, (4) environment in manufacturing – low humidity environments and (5) improving the stability of the core – use of low water activity excipients.

Oral dosage forms are the most preferred and practical route of administration. The oral dosage forms possess several advantages over other dosage forms, such as ease of administration, improved patient experience, and the ability to modify the release of the active pharmaceutical ingredient. Even though oral dosage is the most preferred and practical route of administration, it still presents several challenges to drug delivery. Some of these challenges observed are appearance, hardness, solubility, polymorph, disintegration, stability, dissolution, and physicochemical properties, which are important to improve patient compliance. One of the observed culprits that influence these properties is the presence of moisture.

Management of moisture is a critical aspect of the successful acceptability of the dosage form by patients and the regulatory agency. The impact of moisture on the stability of active pharmaceutical ingredients is known and well documented in the literature. Moisture in a dosage form can be available in bound and free forms. While the bound moisture is harmless, the free moisture causes challenges to the stability of the dosage form as described above.

Water activity (Aw) is a better and alternate way to measure moisture; it provides essential information about the energy or availability of free water in the given product. It is a better way of predicting stability than the total amount of water.

Some of these approaches come with several limitations. Packaging options are very expensive, thereby increasing the burden on patients. Having low relative humidity in manufacturing is expensive; once the product leaves the given environment, it does not allow further protection. Other methods – such as the use of the process without the use of moisture and/or having excipients that have low water activity and/or excipients that scavenge moisture from the formulations – help in improving the stability of the active ingredient in the formulation. This approach is not only user-friendly but also much more economical and effective. These solutions address the moisture sensitivity problem in a wide array of dosage forms.

To address the challenges associated with moisture instability, Roquette, a leader in plant-based nutritional and functional ingredients, is continuously developing a new set of excipients. Table 1 lists the wide portfolio of excipients suitable for various dosage forms and processes. This range of options helps formulators choose the right excipient(s) depending upon the type and process needed to develop the product.

The following are benefits of the Roquette portfolio to address instabilities associated with moisture:

- Enhances stability within the core of APIs
- Suitable for a wide array of processes
- Suitable for a wide array of dosage forms
- Can improve the shelf life of probiotics

Table 1: Typical properties of Roquette portfolio to address moisture sensitive actives.

Product				Protection for water sensitive APIs		Preferred Production Process		Preferred Dosage Form										
Family	Chemistry	Brand		Typical Water Activity (Aw)	Loss on Drying (Not More Than)	Direct Compression	Dry Granulation and Roll compaction	ODT	Swallowable Tablets	Mini-Tablets	Capsules	Effervescent	Suckable	Chewable	Sticks Packs Sprinkles	Extended Release Tablets	Powder for Oral Suspension
Native Starches	Starch		Maize Starch 5%	0.10	5%		x				x						
Modified Starches	Partial Pregelatinized Starch	LYCATAB®	C-LM	0.10	7%	x**	x**		x		x						
			CT-LM			x**	x**		x		x						
Cellulosic	Microcrystalline Cellulose	MICROCEL®	103 SD	0.20	3%		x		x		x						
			112 SD		1.5%	x	x		x		x						
			MC 112		1.5%	x			x		x						
			113 SD		2%		x		x		x						
Co-Processed excipients	Mannitol and Starch	PEARLITOL®	ProTec	0.10	1%	x	x		x		x				x		
			Flash	0.20	3%	x	x		x		x				x		
	Mannitol and HPMC		CR-H	0.30	4%	x	x		x		x					x	
	Starch and lactose	StarLac®*		0.25	3%	x	x		x		x				x		
	Xylitol and Maize Dextrin	XYLISORB®	XTAB 240	0.30	0.5%	x	x		x		x				x		
			XTAB 400	0.30		x	x		x		x						
Polyols	Mannitol	PEARLITOL®	100 SD	0.10	0.5%	x	x	x	x		x	x			x		
			150 SD			x	x	x	x		x	x					
			200 SD			x	x	x	x		x	x					
			200 GT			x	x	x	x	x	x	x					
			C grades				x	x	x		x	x					
			DC grades			x	x	x	x		x	x					
	Maltitol	SweetPearl®	DC grades	0.10	1%	x	x				x	x		x	x		
			C grades				x				x	x		x	x		
	Xylitol	XYLISORB®	Powder grades	0.15	0.5%		x				x		x	x	x		
	Sorbitol	NEOSORB®	C grades	0.20	1.5%		x							x			x
			DC grades	0.30		x	x				x			x			x
			SD grades	0.40		x	x				x		x				x

*StarLac® is a product co-marketed by Meggle AG and Roquette.
**When used with a combination of other plastic and/or brittle excipients

Excipients with Low Water Activity

To improve the stability of the formulation, it is critical to choose the excipients wisely. At Roquette, various excipients are available that have low water activity. The low water activity products help to reduce the water activity of the formulation, thereby improving the stability of the dosage form. These excipients support different processes and at the same time are also useful in various dosage forms. This gives a researcher a set of tools that helps to choose the right excipients depending upon the process and dosage form required. A plot of some Roquette excipients for water activity against flow is represented in figure 1. Products with water activity as low as 0.1 to 0.4 are available. The lower the value, the better the stability of the product. There are products of the same water activity but differing by flow, thus making them suitable for direct compression to roll compaction or dry granulation.

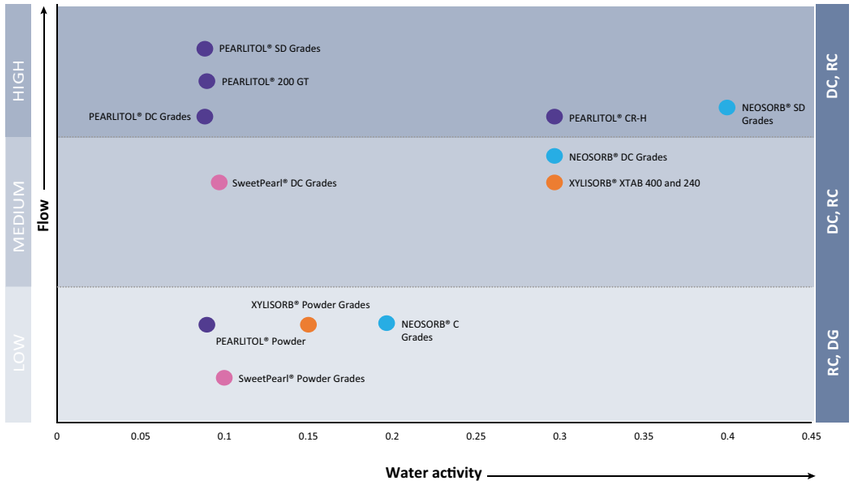

Figure 1: Plot of Roquette's excipient portfolio exhibiting low water activity on water activity versus product flow.

PEARLITOL® mannitol grades with water activity not more than (NMT) 0.1 are available in different flow parameters. The PEARLITOL® spray-dried (SD) grades (PEARLITOL® 100 SD, 150 SD and 200 SD) and PEARLITOL® 200 GT are the grades with superior flow. These are followed by the DC grade (PEARLITOL® 400 DC) and then the powder grades like PEARLITOL® 25 C, 50 C and 160 C. PEARLITOL® mannitol is the most versatile excipient that is suitable for tablets, capsules, sprinkles, sachets, granules and orally disintegrating tablets (ODTs). PEARLITOL® 200 GT, another grade of mannitol, has higher compressibility and can be suitable for mini-tablets, where increasing compression force is a big challenge. It can also be targeted for APIs that show poor compressibility if there is a phenomenon of capping on increasing the compression speeds. PEARLITOL® CR-H co-processed mannitol and hydroxypropyl methylcellulose is another excipient grade suitable for controlled-release tablets, capsules, and powder for oral suspension (PFOS).

If the chemistry of mannitol may not be suitable and formulators need low water activity like 0.1, then products like SweetPearl® maltitol are available. These are supplied with directly compressible (DC) grades exhibiting superior flow, while powder grades are available which are suitable for dry granulation and roll compaction. While PEARLITOL® mannitol grades are suitable for all dosage forms, mannitol is highly suitable for the formulation of ODTs. Both PEARLITOL® mannitol and SweetPearl® maltitol are suitable for immediate release dosage forms.

NEOSORB® sorbitol is available in three different forms such as powders, DC grades and SD grades. As the flow of these products increases, the water activity also increases. The spray-dried grades show water activity of NMT 0.4, the DC grades of NMT 0.3, and the powder grades of NMT 0.2. NEOSORB® sorbitol is a versatile product that can be employed in different processes and is suitable for dosage forms like chewable tablets, sprinkles, sachets, PFOS and granules. XYLISORB® xylitol is available with water activity of NMT 0.15, which makes it suitable for tablets, capsules, sprinkles, granules and sachets, which can be done through roll compaction or dry granulation. If a simple process like blending needs to be employed, then a co-processed excipient of xylitol and maize dextrin like XYLISORB® XTAB (200 or 400) can be employed, which has superior flow in comparison to standard XYLISORB® xylitol.

Excipients with Low Water Activity and Water Scavenging Properties

Low water activity excipients help to reduce the overall water activity in the formulation. However, the lower water activity excipients do not always help. This is due to the free water that may be available in the other excipients or API or can be absorbed during the shelf life of the product. Thus, there is a need for a different set of excipients, which not only have low water activity but also demonstrate water scavenging properties. These excipients bind with water molecules within the dosage forms, which were present or absorbed during the shelf life of the product. This specific preferential interaction of moisture with these excipients reduces the interaction of moisture with the moisture sensitive pharmaceutical actives, thereby improving the stability of the formulation.

Roquette is extensively focusing on this area to help solve the toughest challenges of formulation. Roquette is developing a larger portfolio of excipients which not only offers lower water activity but also water scavenging activity. Roquette recently launched PEARLITOL® ProTec co-processed mannitol and starch, an excipient with a low water activity of NMT 0.1, superior flow and water scavenging properties. It is highly suitable for probiotics, PFOS, tablets, capsules, sprinkles, granules and sachets.

Native starch is a common excipient for manufacturing tablets and capsules. It is a multifunctional excipient with filler, binder and disintegrant properties. However, the standard grades have higher water activity. The maize starch that is further dried helps to offer a lower water activity with water scavenging properties, thus making it possible for usage in tablets and capsules.

Roquette is launching two sets of new products: (1) low moisture partial pregelatinized starch and (2) low moisture microcrystalline cellulose. The details of the same are listed below.

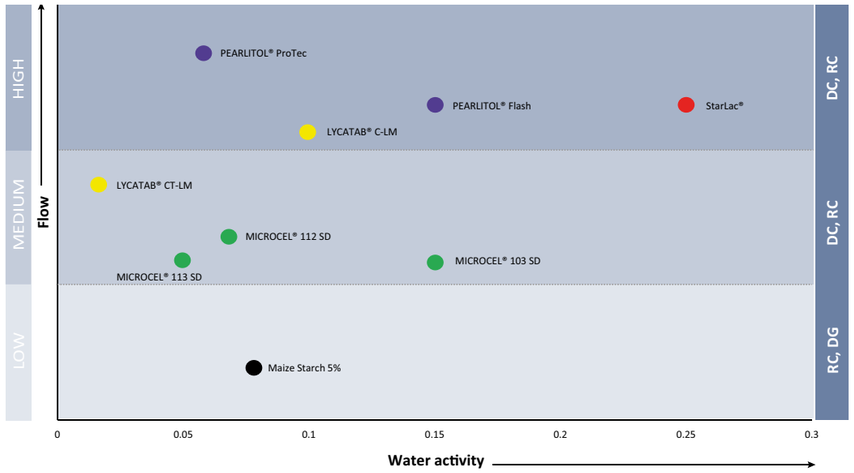

Figure 2: Plot of Roquette's excipient portfolio exhibiting low water activity and water scavenging properties on water activity versus product flow.

LYCATAB® CT-LM partially pregelatinized maize starch with water activity NMT 0.06 is available. It is suitable for tablets, capsules, sprinkles and granules. The very low water activity and the water-scavenging property make it suitable as an ideal filler. Similarly, MICROCEL® 103 SD and MICROCEL® 113 SD microcrystalline cellulose with water activity NMT 0.15 and 0.05 respectively are available. These grades are suitable for tablets, capsules, sprinkles and granules. The very low water activity and the water scavenging property make them suitable as an ideal filler-binder and well suited for roll compaction. When formulating a tablet with direct compression using microcrystalline cellulose as a filler-binder, MICROCEL® 112 SD with water activity NMT 0.06 is available.

As seen above, Roquette offers a portfolio that is suitable for dosage forms like immediate release dosage forms in the form of tablets which can be suckable, swallowable, ODTs, chewable, mini-tablets and controlled release tablets. The portfolio is also suitable for dosage forms like capsules, PFOS, sprinkles, granules, sachets, etc. A detailed discussion of the low moisture grades of partially pregelatinized starch and microcrystalline cellulose is listed below.

Detailed Discussion of Portfolio

Pregelatinized Starches

Pregelatinized starches are produced to ease tasks versus using native starch-like cooking steps or to deliver multiple functionalities (binding and disintegration) with the best level of performance. Through controlled gelatinization, starch is broken into two components: amylose and amylopectin. Amylopectin poses a branched molecular structure that imparts solubility in water, which finally offers binding power. The straight-chain molecular structure of amylose offers strong disintegrating behavior, which is attributed to swelling behavior when it comes in contact with water. These two different properties are captured in one product through a controlled process, which helps LYCATAB® CT-LM and C-LM act as filler, binder, and disintegrant.

LYCATAB® C-LM and LYCATAB® CT-LM are free-flowing powders, used as filler, binder and disintegrant for direct compression in roller compaction, and dry granulation process for manufacturing tablets and capsules. LYCATAB® CT-LM is a new addition to the excipients offered for the protection of moisture sensitive actives. LYCATAB® C-LM and CT-LM reduce the interaction of moisture sensitive actives by bonding preferentially with water that may be present within the product or from the environment during the intended shelf life. This reduces the exposure of APIs to moisture, thereby improving the shelf life.

Table 2: Typical Properties

Test Parameter	LYCATAB® C-LM	LYCATAB® CT-LM
Bulk Density (g/mL)	0.55 – 0.75	0.55 – 0.75
Tap Density (g/mL)	0.70 – 1.05	0.70 – 1.05
Powder Flowability (s)	5	7
Moisture Content	NMT 7%	NMT 7%
Water Activity (Aw)	Less than 0.1	Less than 0.1
Cold Water Solubles	-	10 – 20%
Retained on 425 µm (%)	-	0.5% max
Retained on 200 µm (%)	7% max	-
Passes through 150 µm (%)	-	10% max
Retained on 80 µm (%)	-	-
Passes through 53 µm (%)	-	75% max
Production Site	France	India
Retest Period	24 months	12 months*
Microbial Test	TAMC – NMT 1000 CFU/g TYMC – NMT 100 CFU/g Absence of *E. coli* Absence of *Salmonella*	

* Retest period will be reviewed after additional stability data is available

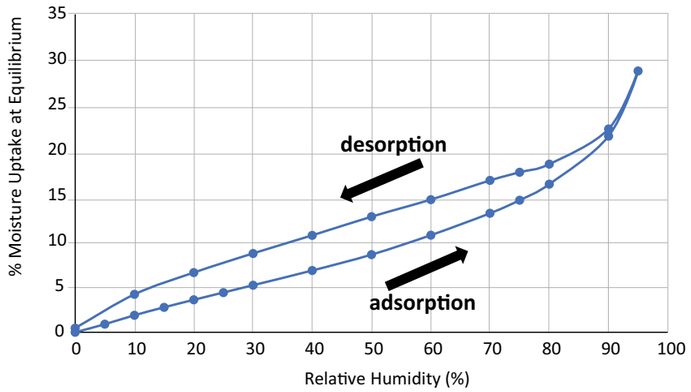

Figure 3: Water sorption of LYCATAB® CT-LM at 25°C

The sorption/desorption isotherms indicate that equilibration was achieved at all humidity levels besides 95% RH (fig. 3). LYCATAB® CT-LM sample can be considered "very hygroscopic" based on the classification as per Ph. Eur. which is defined as >15% w/w sorption at 25 ^{o}C and 80% RH.

Key Benefits

- Manufactured in compliance with IPEC-PQG GMP guidelines in an EXCiPACT™-certified plant, thus giving peace of mind to formulators and purchasers
- Complete documentation and regulatory support, thus helping faster filing and approvals
- Compliance with China DMF, thus helping market extensions and quicker filings
- Halal and kosher certified, thus allowing wider acceptability in the pharmaceutical and nutraceutical market

Microcrystalline cellulose (MCC)

MICROCEL® SD is a partially depolymerized cellulose, white, odorless and tasteless crystalline powder, composed of porous and high compressibility particles. Microcrystalline cellulose is widely used in the pharmaceutical industry in the manufacture of tablets, capsules and others, either in direct compression or in dry and wet granulation processes. Roquette offers eight unique grades of MCC for the most common to complex pharmaceutical formulation needs, which is represented in figure 4.

MICROCEL® 103, 112 and 113 SD microcrystalline cellulose can be used as a filler-binder and fiber source for pharmaceutical oral dosage and nutraceutical forms. These grades have optimized moisture content and compactibility and are primarily used in roll compaction. MICROCEL® 112 SD is also suitable for direct compression in addition to roll compaction. These are spray-dried products produced from an EXCiPACT™ (International Pharmaceutical Excipients Certification) certified plant. Table 3 denotes the typical properties of MICROCEL® 103, 112 and 113 SD.

Table 3: Typical Properties

	MICROCEL® 103 SD	MICROCEL® 112 SD	MICROCEL® 113 SD
Average Particle Size (Microns)	50	100	50
Retained on 60 mesh (%)	NMT 1	NMT 8	NMT 1
Retained on 200 mesh (%)	NLT 30	NLT 45	NLT 30
Loss of drying	3% Max	1.5% Max	2% Max
Bulk density (g/cm3)	0.26-0.31	0.28-0.34	0.27-0.34
D_{10} (microns)	8 – 30	14 – 50	8 – 30
D_{50} (microns)	36 – 75	70 – 140	32 – 78
D_{90} (microns)	80 – 175	160 – 295	80 – 160

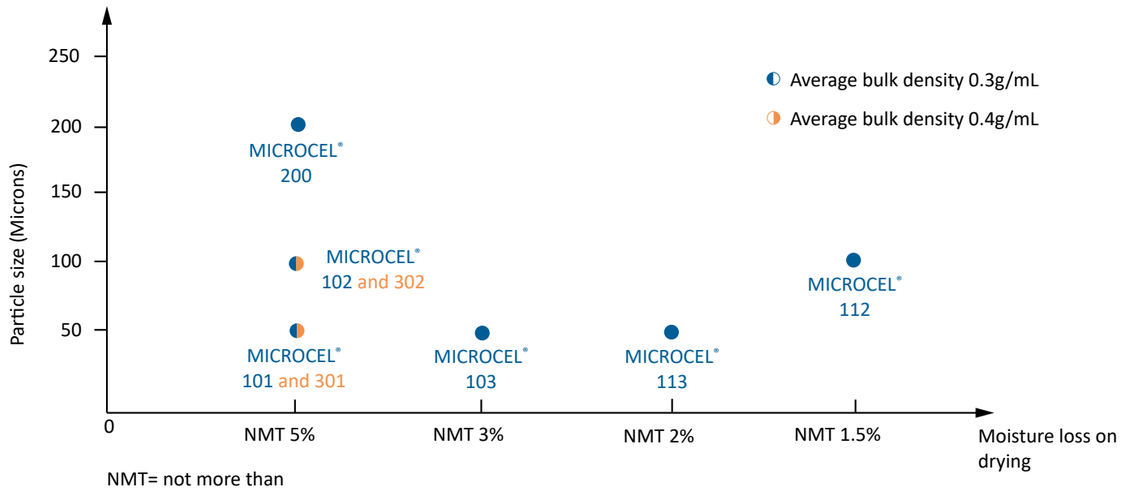

Figure 4: Roquette microcrystalline portfolio.

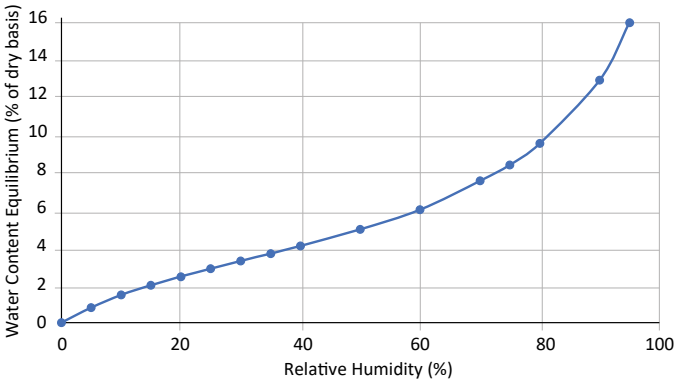

Fig. 5 (a): MICROCEL® 103 SD.

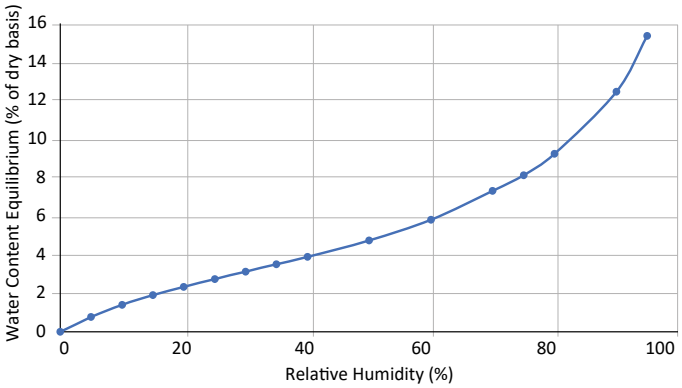

Fig. 5 (b): MICROCEL® 113 SD

Figure 5: Typical water adsorption isotherm of MICROCEL® 103 and 113 SD.

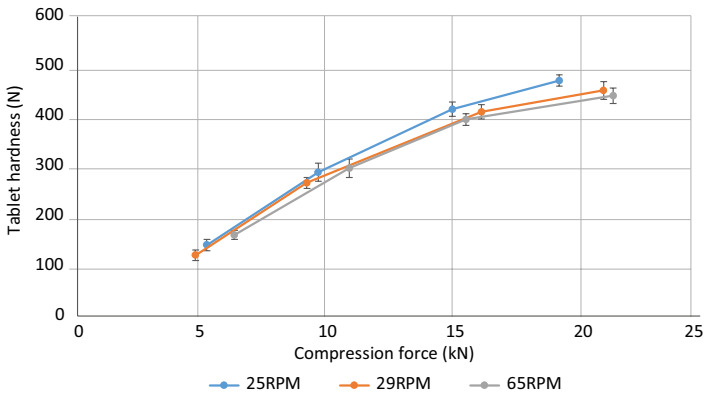

Fig. 6 (a): MICROCEL® 103 SD

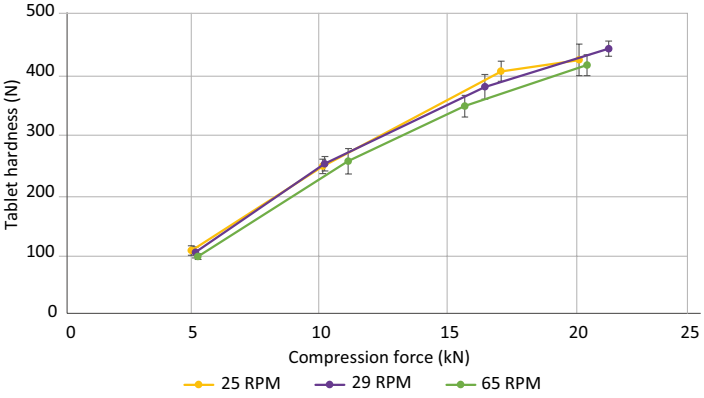

Fig. 6 (b): MICROCEL® 113 SD

Figure 6: Typical compression behavior of MICROCEL® 103 and 113 SD on compression simulator using rotary press simulator.

Figure 2 denotes that MCC does not have the best or the worst flow of the portfolio for the formulation of moisture sensitive actives. It shows optimum acceptable flow. However, MICROCEL® 112 SD has the best flow and lowest moisture content among the three low moisture MCC grades. MICROCEL® 103 and 113 SD are the new products offered in the portfolio. Figure 5a and 5b show that even at high humidity conditions of 75%, the moisture absorption is around 8%, thus making a good choice as a filler-binder in tablets and capsule applications. Figure 6a and 6b indicate that MICROCEL® 103 and 113 SD offer very good hardness, which shows that a minimum of 250 N is achieved at compression forces of 10 KN. These hardness values are independent of the tableting speed employed. The tableting speed has minimal impact on hardness values at a given compression force. Thus, MICROCEL® 103 and 113 SD are well suited for tableting application by roll compaction. MICROCEL® 112 SD is very well suited for tableting applications through direct compression and roll compaction. It is also a preferred filler in capsule application among the MCC grades due to its better flow than the other two low moisture grades.

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For more information, visit our Pharma Virtual Lab:
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