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ORIGINAL ARTICLE

Surrogate functionality of celluloses as tablet excipients

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Abstract

Background: The variety of excipients from different sources and prices to which we have access gives rise to the necessity to evaluate their functional characteristics. The aim of this work is to determine some physical and technological characteristics of celluloses from different sources, India and United States, to ascertain their functionality as tablet excipients. *Methods*: The used surrogate functionality properties are particle morphology and particle size distribution, compactibility, ejection pressure, and the disintegration properties of pure excipients and their compressed tablets. *Results*: The innovators Avicel and Croscarmellose show advantages over the generic celluloses Alfacel and Carmacel. Avicel PH 101 and 102 show an average of 26% greater compactibility than both types of Alfacel, whereas the compactibility of Croscarmellose is greater than that of Carmacel in about 50%. Avicel tablets compacted at a compaction pressure of 47 MPa exhibit shorter disintegration times (3.7 minutes) than Alfacel tablets (28 minutes), whereas Carmacel show better disintegrant properties than Croscarmellose. This occurs regardless of the similar particle morphology, size, and size distribution. As expected, all celluloses show low ejection pressures. *Conclusion*: The surrogate functionality properties of the generic celluloses are still considered as satisfactory to be used as tablet excipients, although they are inferior in some aspects to innovator celluloses. Alfacel and Carmacel have the potential to be used as filler, binder, and disintegrant, in the design of tablets. Moreover, one should bear in mind that the differences reported here may be altered because of a possible inter-batch variability and variations in the moisture content.

Key words: *Alfacel; Avicel; Carmacel; Croscarmellose; direct compression; microcrystalline cellulose; sodium cross-linked carboxymethylcellulose; surrogate tableting properties*

Introduction

The formulation of a tablet is the result of intelligent design and gradual evolution. An optimal formulation is one that is easily manufactured at a range of scales, chemically and physically stable even under adverse storage conditions, globally acceptable to patients and healthcare providers, delivers the active ingredient to the site of action at the optimal rate, and is economically and reproducibly produced using common manufacturing equipment. Moreover, this formulation would probably also contain just a few pharmacopeial excipients that are available from multiple suppliers and which are included with a very specific purpose in mind[1].

Pharmaceutical excipients are a very diverse group of materials. They cover all the states of matter and include materials of both synthetic and natural origin and synthetic or semisynthetic derivatives of some of that of natural origin. Each excipient has its own process and associated know-how. Excipients can also be used in a variety of dosage forms, and some may be used for more than one route of administration[2].

The formulation process requires a clearly defined product profile and information related to the physical and chemical properties of the active ingredient, the physical and chemical properties of the most common excipients, and the operation principles of the manufacturing equipment that is available for commercial production. The active pharmaceutical ingredient (API) properties, such as dose, solubility, compactibility, and so on, are the major constraint on the formulation, and they define how the active ingredient will respond to the stresses of the manufacturing process and its ultimate use by the patient. Once the API properties are fully

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understood, the excipients and the process pathway can be carefully selected to overcome any apparent deficiencies in the API properties. This leverages the unique functionality of each excipient and the benefits of each manufacturing unit operation.

The excipients are included in the formulation because they possess properties that, in conjunction with processing, allow the medicine to be manufactured to meet the required specification. These desirable excipient properties relate to its functional performance or functionality. Functionality is defined as a desirable property of an excipient that aids manufacturing and improves the manufacture, quality, or performance of the drug product. The reality is that functionality can properly be assessed only in the context of the finished pharmaceutical product, and each formulation will have its own particular requirements for functionality. We are thus left with trying to find some surrogate property of the excipient that will allow us to predict whether a particular excipient is likely to have the requisite functionality to produce a product that will meet finished product specifications in all respects. The relevant characteristics will probably be different for each application[2].

Even if excipient functionality can be assessed only in the context of a particular formulation and manufacturing process, certain excipient properties may relate to functionality in a more general sense. The functionality-related characteristics can be considered as surrogates for functionality because they can be measured and limits can be set[3].

For each excipient, for each type of application, and based on the knowledge accumulated over the years of use, we can make a good estimate of which excipient properties, physical or chemical, are likely to be important[4].

Formulators often choose established excipients and processes during formulation development. They opt for traditional excipients even when they are not the most cost-effective materials, and that has direct and indirect impacts on other groups within the organization, particularly manufacturing. These old habits may change as pressure grows to contain costs and as companies face more competition, especially from lower cost manufacturers. One tool to contain costs is using multifunctional excipients that perform the functions of several traditional excipients without the need for complex processing. They integrate time, efficiency, process, and formulation choices early in the development phase. Those choices can pay dividends throughout a product's life cycle[5].

Over the years, significant advances in the manufacturing processes of oral solid dosage forms have occurred, including the transition from tablet preparation by wet granulation to direct compression. The development of various added functionality excipients, which are used to achieve formulations with desired end-effects, is equally important. Added functionality excipients facilitate the development of novel drug delivery methods and improve processing techniques[6].

On a product development basis, excipient manufacturers are responding to demand by pharmaceutical companies for improved performance and multifunctionality. Future demands on excipient technology will continue to be driven by drug industry developments such as new production methods, outsourcing, globalization, and reduced timelines to launch new products. At the same time, there is a growing demand for excipients in emerging markets and imports of low-cost generic excipients into mature markets. All of these forces need to be considered to formulate an effective product, taking into consideration a global excipients market[7].

On a cost basis, the increased competition from generics producers is driving down the price of ingredients. This is forcing excipient companies to readdress their efforts focusing on continually enhancing their good manufacturing practices and developing innovative drug-delivery solutions. Drug manufacturers increasingly are looking toward low-cost excipients to replace their high-cost solutions[8].

Economics plays a role in almost every business decision we make, forcing us to analyze cost versus benefit and supply versus demand. In the pharmaceutical industry, however, some decisions are more a matter of culture or set practice than strict economics, especially when selecting excipients. Selecting excipients for tableted products affects formulation, process development, and commercial manufacturing in ways that are not readily apparent. High-functionality excipients can decrease a company's cost of goods sold and improve profits. High-functionality excipients are multifunctional, performing the functions of several traditional excipients without the need for complex processing.

Today, the development of an appropriate formulation of drug and excipients and of an effective manufacturing process to create a tablet is slowly transforming from a practice of applied art to one of applied science. This will ensure the consistent production of products that meet their specifications and remain safe and effective during their shelf life.

Successful formulation design starts with the collection of adequate preformulation information. Preformulation information denotes the complete set of physical, chemical, technological, and biological data about the API and each excipient that may be incorporated into the drug product. Because each development project is different, it is impossible to provide an exhaustive list of information and data that must be assembled[9].

It is recognized that opportunity and potential has given new life and investment into excipients, which are

not viewed as simply specialty binders and fillers but as functional and performance ingredients. Furthermore, excipients are a key factor to improve the pharmacokinetics and esthetics of pharmaceuticals. Cellulosics such as microcrystalline cellulose (MCC) and sodium cross-linked carboxymethylcellulose are examples of multifunctional excipients. Cellulosics have the potential to be used as filler, binder, and disintegrant, all-in-one, in the design of tablets. Cellulosics hold the top spot in the carbohydrates segment on a value basis. Carbohydrates represent the largest share of global organic excipients on a value basis, accounting for 39%, or $1.2 billion, of the global organic excipient market, based on 2006 data[10].

The functional performance of tablet excipients is related to their physical, chemical, and technological properties. It can be assessed with the excipients as powders, as a dosage form of the pure excipients, and as a formulation of a given drug containing the excipients. The first two levels correspond to a surrogate functionality that belongs to a preformulation phase. The knowledge of the surrogate functionality allows us to predict whether a particular excipient is likely to have the requisite functionality to produce a product that will meet finished product specifications in all respects. The third level corresponds to the explicit functionality of the excipients to develop an appropriate formulation of a drug and an effective manufacturing process to create a tablet.

MCC is purified, partially depolymerized cellulose, prepared by treating α-cellulose with mineral acids. MCC occurs as a white odorless, tasteless, crystalline powder composed of porous particles of an agglomerated product. Apart from its use in direct compression, MCC is used as a diluent in tablets prepared by wet granulation, as filler in capsules, and for the production of spheres. In the pharmaceutical market, MCC is available under the brand names Avicel, Alfacel, Emcocel, Vivacel, and so on.

The types of cellulose have been evaluated as powders for moisture content, packing properties, flow properties, particle size and size distribution, and crystallinity, whereas their tablets as pure excipients or in model formulations have been evaluated for their tableting properties, release profile, and disintegration time. Bhimte and Tayade have found that crystallinity and moisture content were similar for different samples, showing differences in the particle size and size distribution. The powder flow was good for Flocel 102 and Avicel type 102, fair for Ranq 102, and poor for fine powder and sisal fibers. The disintegration time was comparable for Avicel and Flocel whereas Ranq and sisal fibers showed higher disintegration time, however, the release profiles were comparable[11].

Similar parameters were used to compare the two MCCs, Vivacel 101 and 102, against Avicel. The results showed no significant differences in the rheological properties neither in the disintegration times[12]. Moisture content, particle size, powder flow as well as the friction and crushing strength of the tablets have been used to evaluate the comparative tableting properties of 16 samples of MCCs. Great differences in tableting properties were observed between products from the various manufacturers while lot-to-lot variability was quiet acceptable[13]. Parameters such as compactibility and powder flow have also been used to evaluate the functionality of various pharmaceutical lactose powders[14].

The use of mechanical properties to evaluate the functionality of two varieties of MCC, in tests of direct compression hydrochlorothiazide tablets, showed that Avicel PH 102 had better mechanical properties, owing to lower compressibility of mixtures and greater interparticle bonding. In the contrary, Avicel PH 101 tablets released the active principle faster[15]. The tensile strength and the disintegration time have also been used to evaluate different silicified MCCs. Prosolv SMCC 90 proved to be better compactible than Prosolv HD 90. On the contrary, the disintegration time of compacts from Prosolv HD 90 was shorter than from Prosolv SMCC 90[16]. Moreover, silicified MCC has been compared to MCC to address the processing and dissolution of a tablet dosage form of the investigational compound R411. All formulations showed comparable compactibility, however, MCC showed sticking of the lower punches[17].

Cross-linked carboxymethylcellulose is a cross-linked polymer of carboxymethylcellulose sodium. Cross-linking makes it an insoluble, hydrophilic, highly absorbent material, resulting in excellent swelling properties, and its unique fibrous nature gives it excellent water-wicking capabilities. It provides superior drug dissolution and disintegration. In the pharmaceutical market, it is available under the brand names Croscarmellose, Carmacel, Ac-Di-Sol, Primellose, Pharmacel XL, and so on.

Some studies have been undertaken to assess factors influencing superdisintegrants functionality and to evaluate the brand-to-brand variability. Some parameters used to make the evaluation included the particle size, the water uptake, and the swelling properties of the pure excipients as well as the disintegration time of model formulations. It has been concluded that the particle size would be a factor to be taken into consideration for product optimization[18]. By using the water sorption properties as evaluation parameter of superdisintegrants such as Croscarmellose, it has been found that disintegration time of tablets decreased with the increase in water sorption properties of the disintegrants[19]. Although the disintegrant action of the two types of Croscarmellose (Ac-Di-Sol, FMC Corp., Philadelphia, PA, USA and CLD-2, Buckeye Cellulose

Corp., Memphis, TN, USA) showed to be superior to other disintegrants, the CLD-2 may promote more rapid dissolution in some systems than Ac-Di-Sol[20].

Differences in disintegration efficiency of two brands of sodium starch glycolate were found to be related to the purity of the products. The differences, however, were too small to have practical significance and the disintegrants were considered as being pharmaceutically equivalent, when used as disintegrant in tablet formulations[21]. Although differences were observed in the axial and radial disintegration force measurements of the pure disintegrant compacts, disintegration and dissolution of a model drug (hydrochlorothiazide) from either the soluble or the insoluble core did not reveal any significant differences between the multiple sources of sodium starch glycolate[22]. Although the mechanical properties of superdisintegrants are not their primary functionality, these characteristics have been used to assess their functional performance. Three commercial grades of sodium starch glycolate successfully used as disintegrants exhibited differences in their powder mechanical properties: Primojel and Explotab exhibited similar compactibility, whereas Vivastar P was poorly compactable. These observations were considered to be taken into account when formulating poorly compactable drugs[23].

The great variety of excipients from different sources and prices to which we have access thanks to the globalization give rise to the necessity to evaluate the physical, chemical, and technological characteristics of the excipients. Such an evaluation will allow us to compare and select the most convenient excipients for our products.

The aim of this work is, in a first approach, to determine some physical and technological characteristics of MCCs and cross-linked sodium carboxymethylcelluloses from different source, India and United States, to ascertain their functionality and their functional equivalency as tablet excipients, using surrogate functionality properties such as particle morphology, particle size and size distribution of the powders, the compactibility, ejection pressure, and disintegration properties of the pure excipients as compressed tablets.

Materials and methods

Materials

The following were the materials used in this study: MCC, Avicel PH 101, batch P107818846 and PH 102, batch P107818846, FMC Biopolymer; MCC, Alfacel type PH 101, batch 12 and type PH 102, batch 13, Reliance Cellulose Products Limited (Secunderabad, Andhra Pradesh, India); cross-linked carboxymethylcellulose sodium, Croscarmellose sodium, batch T0801C, FMC Biopolymer; and cross-linked carboxymethylcellulose sodium, Carmacel P-(CC), batch 02, Reliance Cellulose Products Limited.

Morphology and particle size analysis

The morphology and particle size has been examined microscopically (National, model DC2-156-S with software Miotic 2000 v. 1.3 National optical & Scientific Instruments, Inc., San Antonio, TX, USA). There are many ways of defining particle size, but only perfect spheres, which are rare in the manufacturing environment, can be described fully using a single number (a diameter). For particles with irregular shapes, there are multiple, equally valid measures. Some authors consider the longest dimension as the most relevant when particles are highly irregular[24]. Certainly, the most commonly used measurements of particle sizes are the length and the width[25]. In this case, it has selected the longest dimension. It has selected a number-based particle size distribution, reporting the number of particles in each size range. In 1 mL mineral oil with a vortex, 100 mg of each excipient was dispersed, examining the morphology and measuring at least 500 particles. The obtained data were treated according to the method of Rosin, Rammbler, Sperling, and Bennett (RRSB), based on the Weibull distribution[26].

Compactibility and ejection pressure

Five hundred milligrams of excipient were compressed for 10 seconds at different compaction pressures in a hydraulic press. The punches were flat with a diameter of 12.8 mm. Tablet crushing strength was measured in triplicate, registering the results as an average. For this purpose, hydraulic presses with a pointer for the maximal pressure reached were used. The procedure was to place each tablet diametrically between two flat surfaces and to apply pressure until the tablet broke. The maximal pressure reached was taken as the tablet hardness. In the same way, the necessary pressure to eject the formed tablets was taken as the ejection pressure. For this purpose, the pressure was applied on a punch while the die was supported on an acrylic cylinder, allowing the tablet release from the die where it was formed.

Disintegration properties

The disintegration test is carried out using the disintegration tester and the procedure described in the Mexican Pharmacopeia[27]. The basket is immersed in a bath of water held at 37°C, in a 1 L beaker. The disintegration time was determined by triplicate, registering the results as an average.

Results and discussion

Morphology and particle size distribution

Pharmaceutical powders can be very different in their particle morphology and size, which can significantly affect their properties. Microscopy is the simplest technique of estimating size ranges and shapes, although it is slow for quantitative determination the material is best observed as a suspension in nondissolving fluid.

The photomicrographs in Figure 1 show the morphology of MCC particles, the innovator Avicel, and the generic Alfacel. Both products present a similar fibrous structure of individual particles, with a plate-like form. Although Avicel and Alfacel exhibit a similar particle structure, they differ from other celluloses such as Ranq-102 and Flocel 102 that contain a good amount of angular, fibrous particles with a few plate-like structures[11]. This is observed by the type PH 101 as well as for the type PH 102.

Figure 2 shows photomicrographs of sodium cross-linked carboxymethylcellulose as the innovator product, Croscarmellose sodium, and the generic Carmacel P-(CC). Both materials show a similar morphology, fibrous and without pores. These materials exhibit a certain degree of curvature along the particles, curvature that seems to be something greater by the generic Carmacel P-(CC). The particle morphology is similar to that observed in scanning electron micrographs of Croscarmellose but different from other superdisintegrants. Sodium starch glycolate particles are spherical and nonporous and crospovidone particles appear highly porous and granular[28].

The particle size distribution of powders may have significant effects on the quality characteristics of the final product. In the case of pharmaceuticals, properties like processability, bioavailability, stability, and content uniformity are influenced to a considerable extent by the particle size. In such instances, the particle size distribution of the powders should be controlled using appropriate analytical methods and proper specifications[29].

A directly compressible adjuvant should have a particle size equivalent to the active ingredients present in the formulation. The particle size distribution should be consistent from batch to batch. Reproducible particle size distribution is necessary to achieve uniform blending with the active ingredient(s) to avoid segregation[30]. In this way, the particle size and its distribution is a reference parameter of excipients used in tableting.

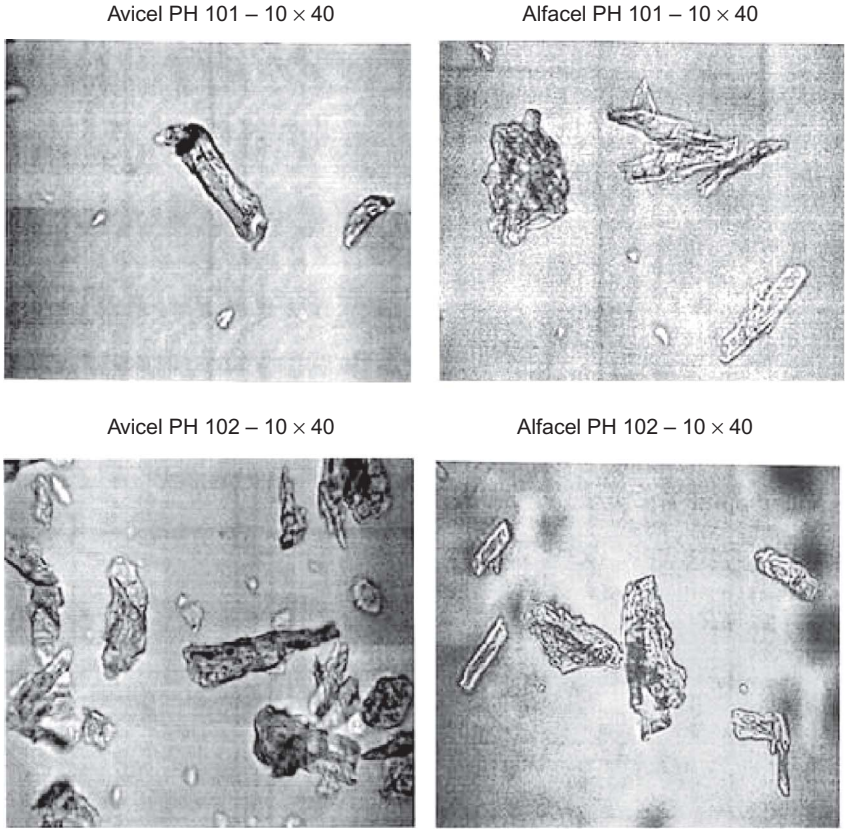

Figure 1. Photomicrographs of different microcrystalline celluloses: Avicel and Alfacel types PH 101 and PH 102 obtained with the program Motic 20001.3.

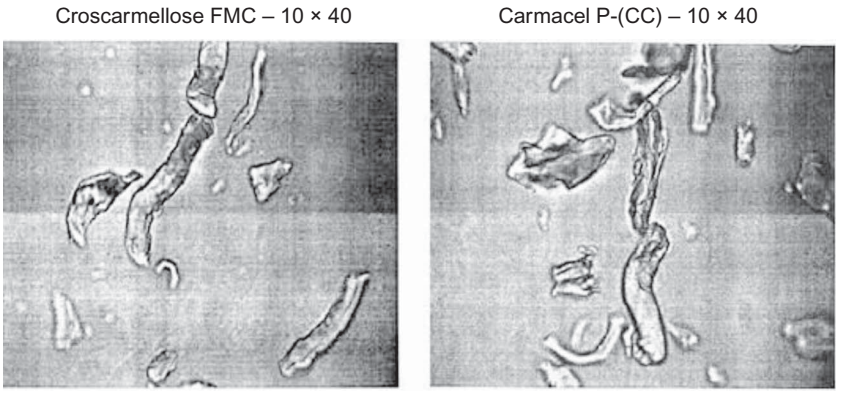

Figure 2. Photomicrographs of Croscarmellose sodium and Carmacel P-(CC) obtained with the program Motic Images 2000 1.3.

The particle size obtained after microscopic observation was divided into classes to obtain a graph of size frequency similar to that showed in Figure 3, taking Alfacel type PH 101 as an example. The distribution of Alfacel particle size shows a shift toward smaller particles, as most particle size distributions from natural origin. In this case, the particle size corresponding to 50% of the cumulated frequency is 57 µm and can be taken as a distribution's size reference. After treating the data according to the RRSB method based on the Weibull distribution (Figure 4), a lineal regression can be obtained that describes the size and dispersion degree of the particle size distribution[26].

The RRSB method allows the description of the particle size distribution with a mathematical equation where the reference for size is the point in the cumulated frequency that divides the distribution into 63.2% of particles smaller than and 36.8% of particles greater than the obtained size value for the diameter. This point is taken as a reference because it corresponds with a zero value of the double logarithm of cumulated frequency expressed as a fraction. This value is designed as d' and in this case corresponds with 68 µm.

An estimate of the dispersion degree of the distribution is the slope of the curve. The greater dispersion of the particle size corresponds with a smaller value of the

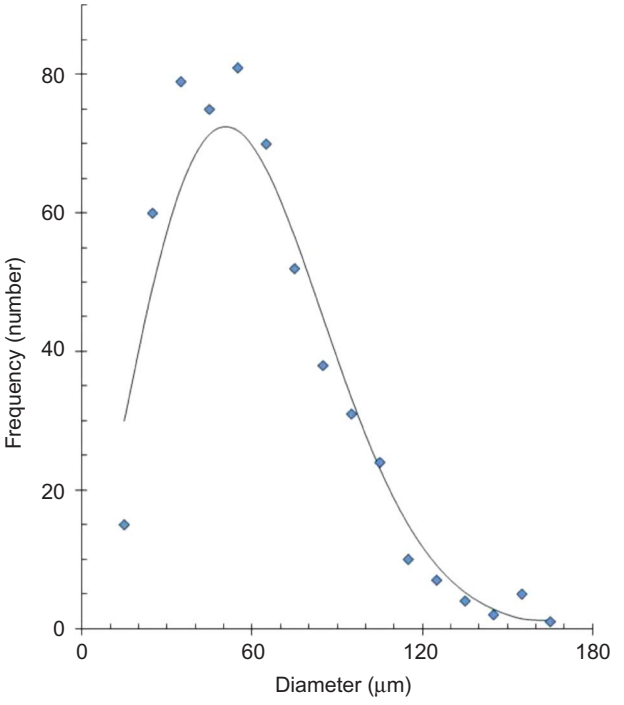

Figure 3. Particle size distribution of Alfacel PH 101 obtained with a sample of 554 particles and using as a reference of size the maximal diameter of each particle.

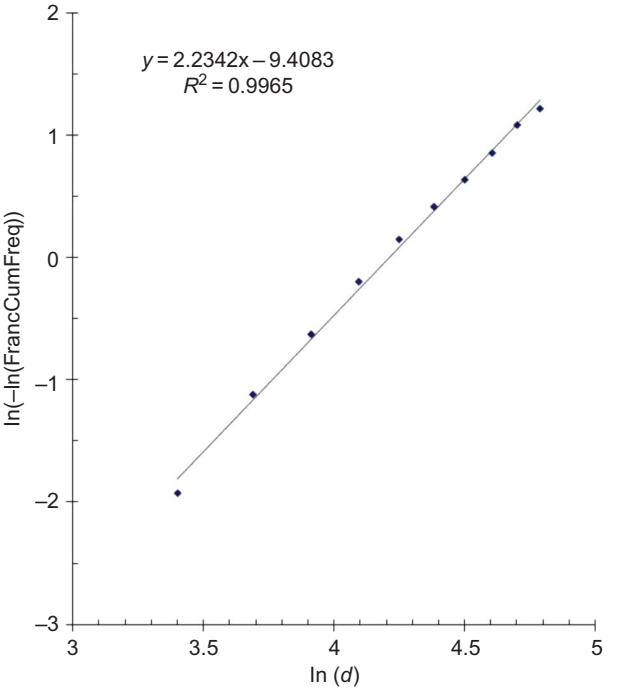

Figure 4. Particle size distribution of Alfacel type PH 101 depicted according to the RRSB method based on the Weibull distribution.

slope and conversely. Equation (1) is used to depict in a graph the experimental points and to calculate the size and the dispersion degree of the size distribution.

$$\ln(-\ln(\text{FracCumFreq})) = n^* \ln d + \text{Constant} \qquad (1)$$

where FracCumFreq denotes the cumulated frequency expressed as a fraction, d the diameter of the particles, n the slope of the curve, and the *Constant* the intercept of the curve.

Considering the particle size distribution of Alfacel type PH 101 (Figure 4), the dispersion degree (D) can be expressed as the inverse of the slope; in this case $D = 0.447$. The above-mentioned equation describes properly the particle size distribution of Alfacel type PH 101, showing a determination coefficient of 0.996. The same procedure was followed to calculate the particle size and its distribution of the four MCCs and the two sodium cross-linked carboxymethylcelluloses. The regression parameters obtained for MCCs are listed in Table 1.

The particle size is, as expected, greater for the types PH 102 than that of the types PH 101. This occurs with all calculated particle diameters along all different proportions of the cumulated size distribution. However, the particle size of the type 102 is not the double of the type 101, as reported in the literature[31]. The particle size of the type 102 is only about 15–30% greater than that of the type 101. Moreover, Alfacel particle size is in every case greater than the Avicel particle size. The dispersion degree is greater by Avicel products than for Alfacel products. Despite the different dispersion degree, both products are consistent with each other. Both types of Avicel show a similar dispersion degree as well as both types of Alfacel. Thus far, no judgment can be made about the pharmaceutical technological significance of these differences in the particle size and its distribution of both types of MCC from both vendors.

Figure 5 depicts the calculated particle size distribution for both types of cellulose from both vendors. It is clear the shift toward smaller particle sizes by Avicel, compared to Alfacel. Although it is not trouble-free to see the calculated smaller particle size of Avicel PH 101, compared to Avicel PH 102. In the case of Alfacel, it is easier to visualize the smaller particle size of the type 101.

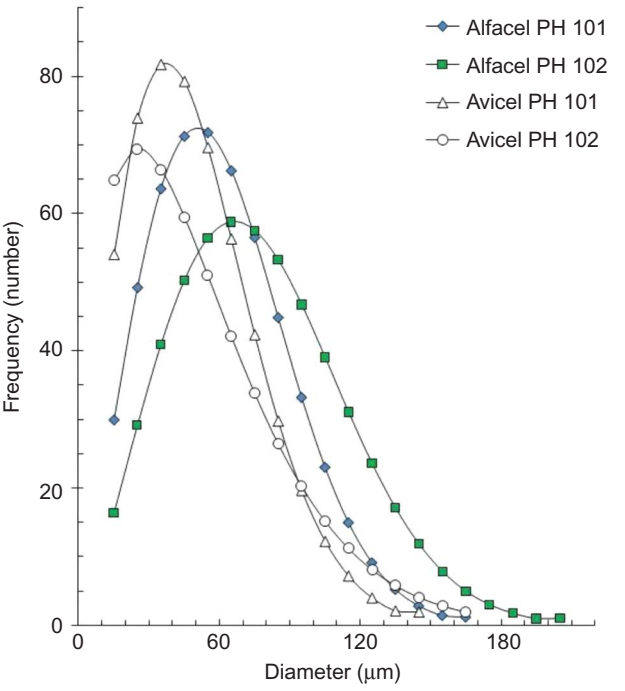

Figure 5. Particle size distribution of microcrystalline celluloses from two different vendors, innovators and generics, calculated for the types PH 101 and PH 102. This was determined with the maximal size of each one of at least 500 particles.

Moreover, it is also not easy to see the smaller dispersion degree of Alfacel particles compared to that of Avicel particles. These circumstances emphasize the need for a mathematical description of the particle size distribution. Anyhow, the particle size distribution can be used as a fingerprint of each product.

The particle size of sodium cross-linked carboxymethylcelluloses, determined in the same way as that of MCC, is depicted in Figure 6. In this case, both products the generic Carmacel P-(CC), and the innovator Croscarmellose, exhibit similar particle size distributions. However, the dispersion degree of the particle size is smaller for Carmacel than for Croscarmellose (Table 2). The dispersion degrees from both sodium cross-linked carboxymethylcelluloses are consistent with those of the MCCs from both vendors (Table 1).

The particle size is a parameter most dependent on the operational definition of the measurement method. In this way, these results can be more or less comparable

Table 1. Particle size and regression parameters of the particle size distribution of two different types and two different vendors of microcrystalline cellulose, calculated according to the RRSB method.

	Particle size (µm)				Regression parameters			
Excipient	d'	$d_{10\%}$	$d_{50\%}$	$d_{90\%}$	n	Constant	r^2	D
Avicel PH 101	57	92	46	15	1.716	−6.927	0.989	0.583
Avicel PH 102	66	105	54	19	1.799	−7.543	0.990	0.556
Alfacel PH 101	67	98	57	25	2.234	−9.408	0.996	0.447
Alfacel PH 102	86	130	76	33	2.243	−10.00	0.999	0.411

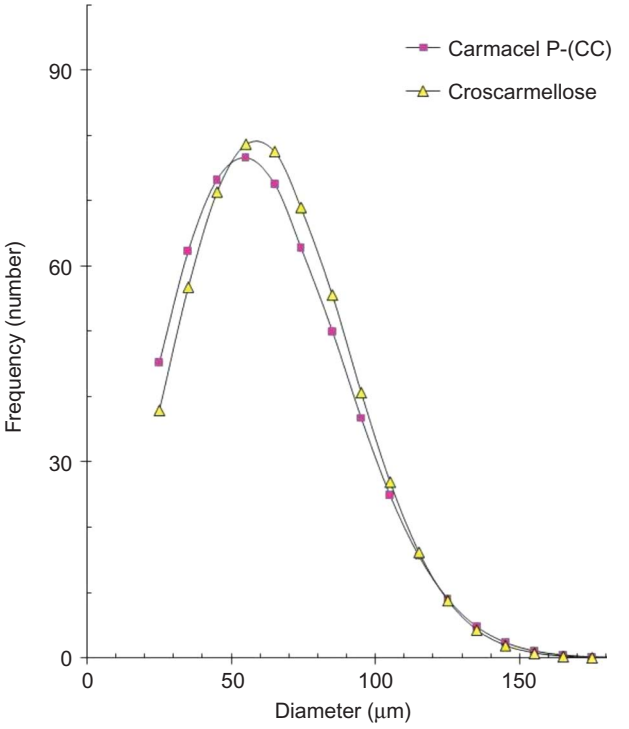

Figure 6. Particle size distribution of sodium cross-linked carboxymethylcelluloses from two different vendors, innovator and generic, calculated according to the RRSB method with at least 500 particles.

to some other reports in the literature. However, some other definitions of particle size can be something imprecise, making difficult the comparison. An example is the particle size definition of Vivapur 102 which is defined as <1% is >250 µm, 58% is >75 µm and 82% is >32 µm[32]. Avicel is described with a particle size of ~50 µm for the type 101 and ~100 µm for the type 102[31]. Although not equal, the actual particle sizes obtained for MCCs type 101 are in the range of that of literature. The same can be said about the sodium cross-linked carboxymethylcelluloses. Croscarmellose sodium is reported with an average particle size of ~50 µm[28,33]. However, the particle size of MCC type 102 was found to be smaller than that reported, ~100 µm[31], 115–153 µm [11].

Compactibility

Direct compression is the preferred method for the preparation of tablets. This circumstance outlines the importance of the functionality of the directly compressible adjuvants in the formulation of tablets. The compaction is a process where pressure is exerted on a material confined on a die, with the purpose to form coherent agglomerates with certain desirable properties. These properties include a defined form, enough mechanical strength, and a greater apparent density than that of the original powders. The mechanical strength of a tablet provides a measure of the bonding potential of the material concerned and this information is useful in the selection of excipients.

The compactibility, defined as the capability of materials to form agglomerates after compression, has been described with Equation (2)[34,35].

$$\ln(-\ln(1-D/D_{max})) = n\ln P_c + I \qquad (2)$$

where D denotes the tablet's hardness or crushing strength, D_{max} the maximal tablet hardness obtained, P_c the compaction pressure, n the slope of the curve, and I the intercept of the curve.

The compactibility of the excipients is defined using the regression parameters of Equation (2). The obtained compactibility curves describe the relationship between the hardness of the tablets and the compaction pressure used to obtain them. Figure 7 shows the experimental data and the compactibility curve for Avicel PH 102, obtained after regression of experimental data. This regression was calculated applying Equation (2) to experimental data. As can be seen, the data can be described properly with the applied model. The lineal regression was obtained from the data depicted in Figure 8, according to Equation (2). The obtained regression parameters are summarized in Table 3.

In general, densification, tensile strength, and hardness increase as the average particle size decreases, and a significant amount of compaction pressure is required for densification to occur. However, these effects present a potential problem when compacting particles that are very small[36].

The effect of particle size on the compactibility of pharmaceutical powders seems to be different in different materials as well as in materials from different source. It has been observed that a smaller particle size of MCC produces tablets with higher hardness[30]. Tablets containing higher percentage of Avicel PH 101 exhibited higher crushing strength, whereas the tablets containing Avicel PH 102 and PH 200 showed lower

Table 2. Particle size and regression parameters of the particle size distribution of sodium cross-linked carboxymethylcelluloses from two different vendors, calculated according to the RRSB method.

	Particle size (µm)				Regression parameters			
Excipient	d'	$d_{10\%}$	$d_{50\%}$	$d_{90\%}$	n	Constant	r^2	D
Croscarmellose	72	101	62	29	2.4876	−10.64	0.977	0.402
Carmacel P-(CC)	70	108	58	22	1.9511	−8.293	0.992	0.512

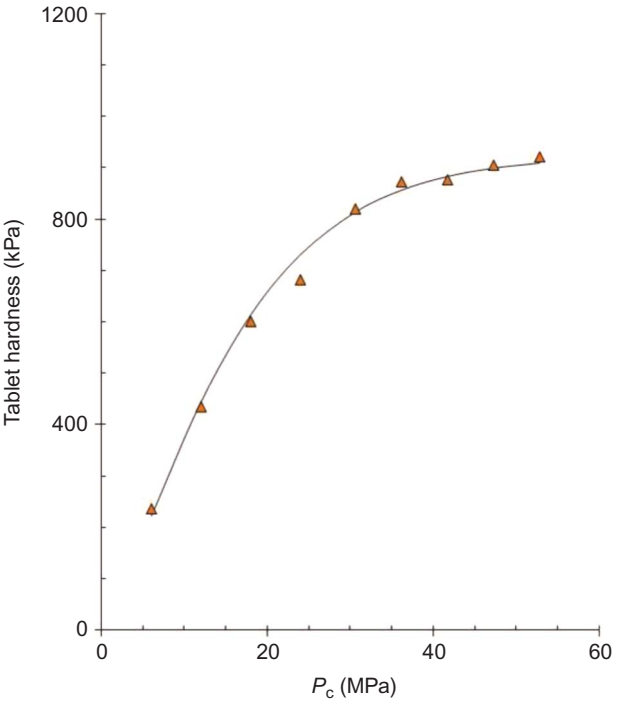

Figure 7. Compactibility curve of Avicel PH 102. Tablets of 12.8 mm and a weight of 500 mg. The points are experimental and the curve is the calculated regression.

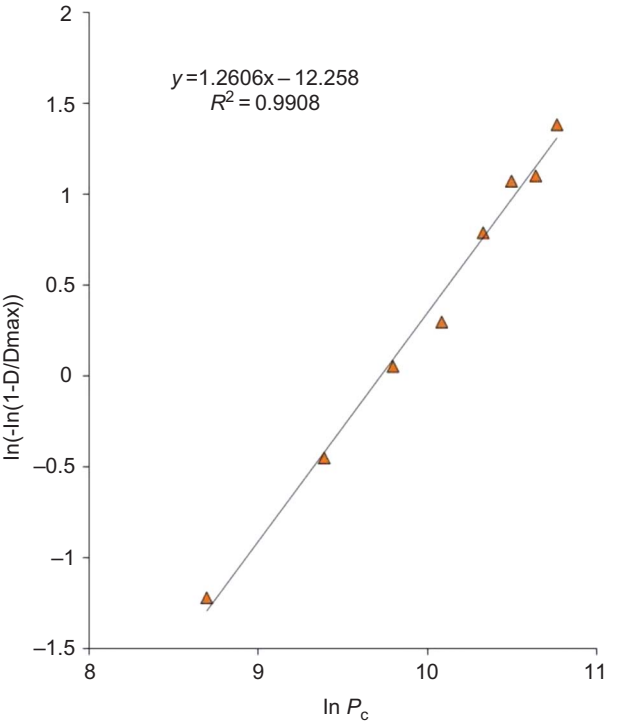

Figure 8. Compactibility curve of Avicel PH 102. Tablets of 12.8 mm and a weight of 500 mg. Data adjusted according to Equation (2).

crushing strength[37,38]. In the same sense, it has been suggested that the finer MCC particles (e.g., Vivapur 102, 58% particles are >75 µm) have larger surface areas with which to contact each other, resulting in higher hardness values. Vivapur 102 tablets showed 36–63% higher tablet hardness than Vivapur 12 (45% particles is >160 µm)[32].

Despite that, in a short version of the comparative properties of various grades of Avicel, Avicel PH 102 has been described as having large particle size and similar compression properties as Avicel PH 101. In the same way, Avicel PH 200 (~180 µm) has been described having a large particle size which offers increased flowability with a minimum effect on compression characteristics[37]. In a study about the effect of particle and powder properties on the mechanical properties of directly compressed cellulose tablets, it was found that the most important material property affecting the breaking strength of tablets was the specific surface area of the starting material. No correlation between crystallinity, particle size or particle shape of the starting material and the strength of tablets was observed[39]. Furthermore, in a study about the compactibility of materials with different particle size, different size fractions obtained from MCC type 101, showed slightly increasing tablet hardness with an increasing particle size[40].

Table 3. Calculated regression parameters of compactibility curves for microcrystalline celluloses, innovators, and generics.

Excipient	Dmax (kPa)	Slope (n)	Intercept (I)	r^2
Avicel PH 101	958	1.3262	−3.6707	0.9705
Avicel PH 102	900	1.2606	−12.258	0.9908
Alfacel PH 101	728	1.3668	−4.0836	0.9809
Alfacel PH 102	742	1.2353	−0.385	0.9438

The above-mentioned higher compactibility of smaller particle size MCC is confirmed by compactibility curves of Avicel. Avicel PH 101 shows a higher value of D_{max} (958 kPa) while that of Avicel PH 102 is lower (900 kPa). Although this is the case for Avicel types 101 and 102, this cannot be observed by Alfacel particles (Table 3). Alfacel type 101 shows a lower value of D_{max} (728 kPa) while that of Alfacel type 102 is something higher (742 kPa).

Considering as a reference the maximal tablet hardness reached by tablets of each excipient, Avicel PH 101 shows the maximal compactibility, followed by Avicel PH 102, Alfacel type PH 102 and finally, with the lower compactibility, Alfacel type PH 101. A comparison of the compactibility with the particle size determined by microscopy (Table 1, Figure 5) does not show a consistent relationship. On the contrary, it is clear that both types of Avicel show a greater compactibility than both types of Alfacel, about an average of 26 %.

The compactibility of sodium cross-linked carboxymethylcelluloses and the corresponding regression parameters are summarized in Table 4. Although

Table 4. Regression parameter of compactibility curves calculated for sodium cross-linked carboxymethylcelluloses, innovator and generic.

Excipient	Dmax (kPa)	Slope (n)	Intercept (I)	r^2
Croscarmellose	474	1.9054	−19.644	0.9551
Carmacel P-(CC)	317	1.2969	−13.702	0.9438

sodium cross-linked carboxymethylcellulose is considered as a superdisintegrant, it can also contribute to the mechanical properties of the tablets in direct compression processes. As can be seen in table 4, the compactibility of Croscarmellose (D_{max} = 474 kPa) is greater than that of Carmacel (D_{max} = 317 kPa) in about 50%. Moreover, the slope of the Croscarmellose compactibility curve is also greater. This means a faster increase of the tablet hardness as the compaction pressure increases.

In fact, the compactibility of cross-linked carboxymethylcellulose does not allow a continuous improvement of drug dissolution with increasing proportions of the disintegrant in the formulation. As a reference the percent norfloxacin released after 30 minutes, it has been observed that 2.5% cross-linked carboxymethylcellulose allows the release of 100% of the drug whereas greater proportions of the disintegrant reduce gradually the norfloxacin dissolved up to 76.5% by 6% of disintegrant in the formulation. This effect was attributed to the binding properties of cross-linked carboxymethylcellulose. Disintegrant proportions lower than 2.5% produce an effect of improving dissolution while by higher proportions predominate the effect of the binding properties[41]. Anyhow, the superior compactibility of Croscarmellose would allow the use of lower compaction pressures or lower disintegrant proportions to reach the same compactibility of those tablets containing Carmacel.

Tablets disintegration

For a drug to be absorbed from a solid dosage form after oral administration, it must first be in solution, and the first important step toward this condition is usually the break-up of the tablet, a process known as disintegration. The disintegration test is a measure of the time required under a given set of conditions for a group of tablets to disintegrate into particles, which will pass through a 10 mesh screen. Generally, the test is useful as a quality assurance tool for conventional dosage forms.

Although disintegrants are important components in solid dosage forms, their mechanism of action has not been clearly elucidated. The mechanisms proposed in the past include water wicking, swelling, deformation recovery, repulsion, and heat of wetting. It seems likely that no single mechanism can explain the complex behavior of the disintegrants. However, each of these proposed mechanisms provides some understanding of different aspects of disintegrant action.

Both the rate and force of disintegrant action may be dependent on the particle size of the disintegrant. It has been found that starch grains having relatively large particle sizes were more efficient than the smaller particle size grades. Moreover, results for other disintegrants, Amberlite IRP88w and potato starch, support that coarser particle sizes allow more efficient disintegration than finer particles. This is probably because the continuous hydrophilic network of disintegrants is more efficiently accomplished by the bigger particles. However, disintegrants such as crospovidone not always show this trend toward more efficient disintegration with greater particles[42].

MCC and some products derived from cellulose can be considered as multifunctional excipients for solid dosage forms, especially for tablets; providing characteristics of a disintegrant, diluent, direct compression binder, and lubricant[31].

Despite of a greater compactibility of Avicel products and a greater particle size of Alfacel, Alfacel tablets show greater disintegration times. This can be seen in Figure 9. At low compaction pressures (6 MPa), the disintegration times are quite small, in a range of seconds, and no trend or clear difference between types of cellulose and vendors can be observed (Figure 9). However,

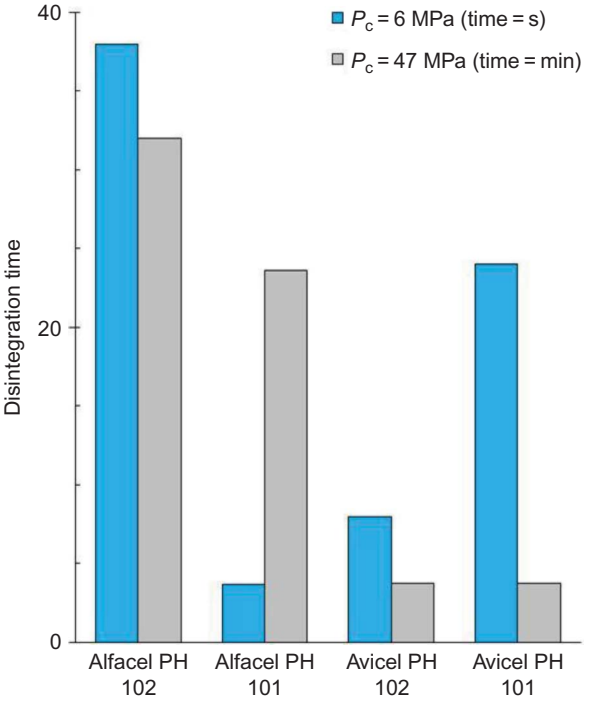

Figure 9. Disintegration time of microcrystalline cellulose tablets of the innovator and the generic vendors and of the types PH 101 and 102, obtained at two compaction pressures, 6 and 47 MPa.

at higher compaction pressures (47 MPa) Avicel tablets show clearly shorter disintegration times than Alfacel tablets. Avicel tablets exhibit an average disintegration

time of 3.7 minutes whereas Alfacel tablets exhibit an average disintegration time of 28 minutes. Moreover, a trend toward shorter disintegration times for celluloses type 102 could not be observed. Alfacel tablets of the type 101 display shorter disintegration times than those of the type 102. On the contrary, Avicel tablets of the types 101 and 102 exhibit similar disintegration times.

The disintegration characteristics of Avicel tablets are much better than that of Alfacel tablets, in spite of the greater compactibility or greater tablet hardness of Avicel tablets (Table 3).

In the case of cross-linked carboxymethylcellulose, the disintegration times obtained from tablets compacted at three different compaction pressures are depicted in Figure 10, including the disintegration time of Avicel PH 101 as a comparison reference. All disintegration times are short, in a range of 4 minutes. At all compaction pressures, the disintegrations times for Croscarmellose tablets are longer than Carmacel tablets. At a first glance, it seems that the longer disintegration times of Croscarmellose are the consequence of its greater compactibility (Table 4). However, the tablet hardness of the tablets obtained at compaction pressures up to 20 MPa are similar, and then, the shorter disintegration times cannot be only attributed to higher tablet hardness. Despite that, the greater binding properties of Croscarmellose are yet considered a factor contributing to the higher disintegration times of its tablets. Although all cross-linked carboxymethylcellulose tablets exhibit short disintegration times, Carmacel seems to have something better disintegrant properties than Croscarmellose.

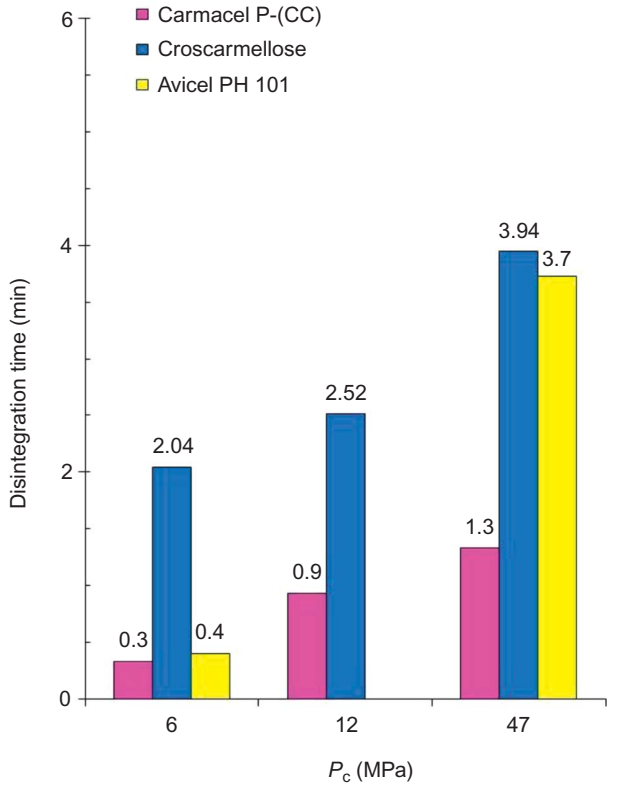

Figure 10. Disintegration time of cross-linked carboxymethylcellulose tablets, innovator and generic, obtained at different compaction pressures (P_c).

Ejection pressure

Apart from the compactibility properties of powders to be compacted as tablets, there are some other powders properties that are involved in the tablet manufacturing process. The friction properties are unimportant if they are low, however, if the powders friction is high may cause some tableting problems such as lamination, abrasion on the tablet surfaces or the impossibility to eject the tablets from the matrix they were compacted.

The lubricants, as tableting adjuvants, became necessary in the formulation of tablets since they are produced in the industry. The lubricants are used to reduce the interparticle friction as well as the friction between the particles and the die wall and punch surfaces. In this way, they facilitate the compression and the ejection of the tablets from the die.

MCC tablets exhibit such a low coefficient of friction that they may need no lubricant. Avicel has an extremely low coefficient of friction, both static and dynamic, so that it has no lubricant requirement itself. It has some self-lubricating properties but addition of a lubricant is usually necessary. It is considered that when more than 20% of the drug and other excipients are added, lubrication is necessary[43].

The ejection pressure obtained for MCC tablets is depicted in Figure 11. The average ejection pressure for Alfacel types PH 101 and 102 is 118 kPa whereas that for Avicel types PH 101 and 102 is 119 and 101 kPa respectively. Although Avicel PH 102 shows a something smaller ejection pressure, the ejection pressures cannot be considered really different. As could be expected, all MCC tablets are easily released from the die they were compacted and the differences are considered irrelevant.

The average ejection pressure for Carmacel and Croscarmellose is similar (130 kPa). As can be seen in Figure 11, put side by side with the ejection pressure of MCC tablets, the pressure needed to release the tablets made of cross-linked carboxymethylcelluloses is 10 kPa greater than that used to release tablets made of MCCs. Practically, the ejection pressure of cross-linked carboxymethylcelluloses is similar to that of MCCs, the differences are quite small.

The ejection pressure of the tablets obtained with different celluloses shows that all of them are easily released from the die they were compacted. Studying the influence of moisture content on the mechanical

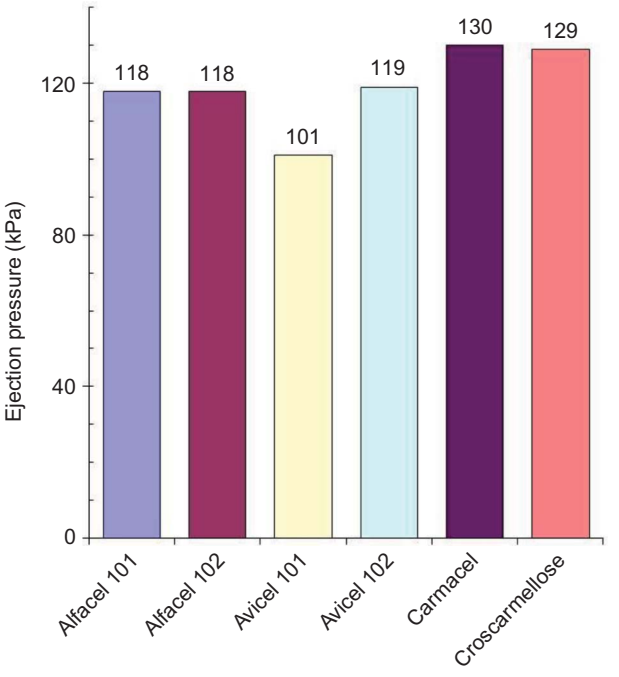

Figure 11. Average ejection pressure of tablets made of different microcrystalline celluloses, of the types PH 101 and 102 and different sodium cross-linked carboxymethylcelluloses. The ejection pressure was determined for tablets compacted at compaction pressures in a range of 6–70 MPa.

properties of methyl methacrylate–starch copolymers it has been observed that the absorbed water might act as plasticizer and adsorbed water as lubricant[44]. Moreover, increasing moisture content up to about 2.5% progressively increased compact strength probably due to the hydrodynamic lubrication effects of moisture promoting optimum transmission and utilization of compaction force[45]. The influence of moisture content and compression speed on the ejection force, plastic and elastic energies of ibuprofen was measured. It was found that moisture could significantly reduce the force required to initiate ejection by the breaking of tablet/die-wall adhesions. An increase in moisture content resulted in a marked reduction in the ejection force of ibuprofen compacts[46].

It has been observed that the effect of water on the mechanical properties of compacts depend on the nature of its interaction with the solids. Water can be included in the crystal lattice, absorbed, adsorbed or included as free water. Studying lactose, MCC, starch, and polyvinylpyrrolidone (PVP), it was found that the ejection pressure decreased as the moisture content increased. However, after certain moisture content PVP became adhesive, presumably due to partial PVP dissolution, increasing the ejection pressure[47]. In this sense, the self-lubricant properties of the celluloses are attributed to their moisture content ≤ 5% and water insolubility.

In the same way, tablets obtained from cross-linked carboxymethylcelluloses are also easily released from the die they were compacted because of their physical characteristics similar to MCCs. The something higher ejection pressures observed by cross-linked carboxymethylcelluloses may be due to their content in water soluble materials (≤10% or between 1% and 10%)[31].

Conclusions

Quality means those features of products that meet customer needs and thereby provide customer satisfaction. For pharmaceutical excipients, the needs are conformance to specification, manufacture to appropriate standards of good manufacturing practice, satisfactory performance (functionality), and customer satisfaction. Because performance or functionality can only be truly assessed in the application, that is, in the manufacture of the medicinal finished product, surrogate tests are required that are predictive of ultimate performance required of the excipient.

The innovator celluloses show advantages as raw materials over the generic celluloses, using surrogate or substitute tests of functionality, regardless of similar particle morphology, size, and size distribution. Despite this, the properties of the generic celluloses are still considered as satisfactory to be used as tablet excipients. The generic celluloses are much superior to some other excipients used with the same purpose (e.g., lactose, dicalcium phosphate), although they are inferior in some aspects to innovator celluloses.

Excipients such as celluloses are multifunctional, performing the functions of several traditional excipients without the need of complex processing. Current results conclusively show that Alfacel and Carmacel have the potential to be used as multifunctional excipients, as filler, binder, and disintegrant, all-in-one, in the design of tablets. Additionally, one should bear in mind that the differences reported here may not be significant because of possible inter-batch variability.

As the results show, celluloses from different source can exhibit a range of tableting properties, and so the substitution of one brand by another must be approached with caution. Moreover, the celluloses are quite hygroscopic, and their tableting properties are dependent on the moisture content. Therefore, comparisons between different brands must also take the moisture content into account.

Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this paper.

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