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Functionality of GalenIQ 721 as excipient for direct compression tablets

Sonia Cecilia Barrios-Vazquez[1], Leopoldo Villafuerte-Robles[1*]
[1]Department of Pharmacy, National School of Biological Sciences, National Polytechnic Institute of Mexico, D. F., Mexico.

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ABSTRACT

The purpose of the work is the comparative evaluation of GalenIQ 721, against known excipients such as Pharmatose M200 and Alfacel type 102. The evaluated parameters included compactibility curves, tablet ejection pressure, disintegration time and flowability of individual powders and mixtures of the excipients and amoxicillin. The surrogate and explicit compactibility of Alfacel 102 (492 N; 7.9 N) is superior, followed by GalenIQ 721 (310 N; 0.93 N) and Pharmatose M200 (203 N; -2.8 N). The lubricity of Alfacel 102 is superior (ejection pressure - Pe=0.590 MPa), followed by GalenIQ 721 (Pe=6.45 MPa) and Pharmatose M200 (Pe=6.51 MPa). Disintegrability of tablets was better by GalenIQ (0.33 s/N), followed by Alfacel 102 (2.48 s/N) and Pharmatose M200 (4.47 s/N).GalenIQ 721 displays a powder fluidity of (14.4 g/s), followed by Alfacel 102 (7.88 g/s) and Pharmatose M200 (0.99 g/s). The tableting functionality of GalenIQ 721 is better than that of Pharmatose M200 but inferior of that of Alfacel 102. Although the GalenIQ 721 characteristics, predominantly brittle, are expected to be more stable to changes in formula composition and process conditions than those of Alfacel 102, plastic behavior.

INTRODUCTION

Tablet production is an essential operation for the pharmaceutical industry. Tablet presses operating on the principle of direct compression have been functioning since decades. However, formulations that process well in these units to consistently deliver uniform tablets with the required properties remain an ongoing challenge. Producing good quality tablets requires manipulation of variables such as particle size and shape, surface texture and moisture content, to control both compactibility and the flow properties of the blend. Excipients are often used to enhance drug properties and processability. The aim is to develop a formulation with optimal rheology that delivers high quality in combination with high productivity. Direct compression involves feeding of tablet ingredients to a press as a blended powder. The blend contains various components such as filler, binder, active pharmaceutical ingredient (API), and lubricant; each of which fulfils a different function in terms of tablet or processing performance. Tablet quality is quantified in terms such as strength, weight, dimensions, and API content, the required properties being produced through control of variables such as flowability and tabletability of the mix. This is achieved by addressing fundamental issues such as excipient choice and the concentration of each component in the final formulation. The API properties are a major constraint on the formulation. The excipients and the process pathway are selected to overcome any apparent deficiencies in the API properties. This leverages the functionality of each excipient and the benefits of each manufacturing unit operation (Hancock, 2009). Excipients are a very diverse group of materials with a diverse range of properties. They are included in many different products to impart several different types of functionality, depending on a particular type of application. Functionality has been defined as a desirable property of a material that aids manufacturing and improves the manufacture, quality or performance of the drug product. In the context of pharmaceutical formulations and products, each formulation will have its own peculiar requirements for functionality. An approach to verify the excipient functionality is to identify a surrogate test that bears some relation to the required functionality. Such properties have been also defined as functionality related characteristics or performance tests (Moreton, 2006).

** Corresponding Author*
Departamento de Farmacia, Escuela Nacional de Ciencias Biológicas, Instituto Politécnico Nacional de México Av. Wilfrido Massieu s/n esq. M. Stampa, Unidad Profesional Adolfo López Mateos. Col. Industrial Vallejo, C. P. 07738, D. F. México.

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 allow us to predict whether or not 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 (Díaz and Villafuerte, 2010).

The selection of the properties to define excipient functionality becomes a critical activity. In the dosage form development this selection is defined as design space. The design space is defined as the multidimensional combination and interaction of input variables (e.g. material attributes) and process parameters that have been demonstrated to provide assurance of quality (Moreton, 2006). The availability of many powder testing methods underlines the difficulties to define powder properties. Many methods have limited value, especially with respect to process development because they capture only one aspect of powder behavior, do not simulate the conditions powders observe in processing, produce data that does not correlate directly with process performance or because they are poorly defined so results are not repeatable or reproducible (Freeman, 2009).

The testing methods used to evaluate the functionality of tableting excipients include physical properties such as bulk density, tap density, Carr index, particle size distribution, surface morphology and thermal properties. They include also technological properties such as tableting properties (Chinta *et al.*, 2009). Tableting parameters include crushing strength, friability and disintegration time (Schmidt and Rubensdörfer, 1994). Tableting properties have been employed to evaluate excipient functionality, considering pre-, during and post-compaction parameters (Çelik and Okutgen, 1993).

Excipients have been evaluated using also the density, powder flow rate and the tableting and the drug dissolution properties with a model drug. This was made considering that the full characterization of excipients is needed because a different manufacturing process for the same excipients may produce differences in the pharmaceutical products (Olmo and Ghaly, 1998). More recently functionality of celluloses as tablet excipients has been evaluated using technological characteristics or performance tests such as compactibility curves, ejection pressure curves, and the disintegration properties of pure excipients as compressed tablets (Díaz and Villafuerte, 2010).

From another point of view, many excipients are considered multifunctional. They are used to provide added functionalities to the formulation. The term multifunctional excipient is also extended to products that serve multiple roles in the formulation, for example, serves the role of direct compression diluents with binder and disintegrant properties (Patel, 2009). In this way, the evaluation of multifunctionality becomes more complex, compared to evaluation of monofunctional excipients, if that really exists.

The usefulness of functionality tests include: a) assessment of materials properties with quality control purposes, b) prediction of a material performance in a formulation, from surrogate functionality tests and functionality of materials in other formulations and c) comparison of functionality of excipients from different source and different physical or chemical characteristics (Villafuerte, 2011).

Among the more frequently used excipients lactose monohydrate is a natural product, is water soluble and is available from many suppliers in a variety of particle size ranges. However, for lactose monohydrate, the tomahawk crystal shape cannot be easily modified. Furthermore, lactose may interact with drug/protein functional groups due to its reducing sugar function (Train *et al.*, 2006).

Lactose is highly reactive, particularly in the presence of active components having primary amino groups. It is known that vitamin D_3 derivatives in particular are remarkably decomposed when blended with lactose. Moreover, when the active components are acid, lactose has a disadvantage of disaccharide to be transformed on hydrolysis into glucose and galactose, losing the properties of lactose (Satomi and Imaoka, 20011).

Pharmatose M200 is a milled lactose monohydrate, most popularly used as filler in tablet production, displays a specific particle size distribution. Up to 90% of the product has a particle size under 100 µm. The small particles and high surface area allow a good wettability and compactibility. It is used as filler for capsules and other solid dosage forms (DMV-Fonterra, 2011).

GalenIQ 721 is an agglomerated spherical isomalt for direct compression applications. Chemically it is a disaccharide alcohol in a 3:1 ratio of 6-O-α-D-glucopyranosyl-D-sorbitol and 6-O-α-D-glucopyranosyl-D-mannitol dihydrate. It is considered agglomerate requiring very low compression forces. The preferred applications are tableting and capsule filling, recommending a minimum of 25% to enhance the tablet hardness in a formulation (Beneo Palatinit, 2011).

Particularly in tableting, the direct compressible isomalt grades 720 and 721 are an alternative to traditionally used bulk excipients because they are multifunctional as filler and binder. Their high dilution potential and morphology ease the development of dosage forms. High-agglomerate stability and superior flow properties facilitate isomalt handling in the tableting process. These two grades differ in solubility producing tablet formulations with different disintegration times (Babel and Fritzsching, 2009).

The comparison of compressibility of the two directly compressible isomalts GalenIQ 720 and GalenIQ 721, using the energy evaluation of the compaction process, showed that GalenIQ 720 is better compressible than GalenIQ 721 (Muzíková and Pavlasová, 2011).

Microcrystalline cellulose is basically cellulose, a naturally occurring polymer; it is comprised of glucose units connected by a 1-4 beta glycosidic bond. Microcrystalline Cellulose is hardly a new product. As a naturally occurring substance, it has proven to be stable, safe and physiologically inert. Microcrystalline Cellulose revolutionized tableting because of its compressibility and carrying capacity. It compacts well under minimum compression pressures, has high binding capability, and creates tablets that are extremely hard, stable, yet disintegrate rapidly. Other advantages include low friability, inherent lubricity, and the highest dilution potential of all binders. These properties make Microcrystalline Cellulose particularly valuable as a filler and binder for formulations prepared by direct compression (NB's Sancel, 2011).

The aim of this work is the comparative evaluation of the GalenIQ 721 functionality as excipient for direct compression, using as reference the excipients lactose (Pharmatose M200) and microcrystalline cellulose (Alfacel type 102) and as evaluation tests the compactibility, ejection pressure, disintegration time and powder flow.

MATERIAL AND METHODS

Material

The materials used in this study were microcrystalline cellulose, Alfacel type PH 102, batch 13, Reliance Cellulose Products Limited, India; Amoxicillin trihydrate, batch MB2433, Química Alkano, Mexico; GalenIQ, batch L631, Palatinit GmbH, Germany and α-lactose monohydrate, Pharmatose M200, batch 024229, Helm-Mexico. The drug and the excipients were used as received. The drug and the excipients were evaluated as individual powders and as mixtures of the drug with each one of the excipients at proportions of 20%, 25% and 50%. The materials corresponding to each formula were sieved (sieve number 20) prior to be mixed. The drug and the excipient were mixed in a twin shell blender for 30 min.

Preparation of Tablets

Tablets of 500 mg each were prepared with a hydraulic press equipped with a manometer and circular (diameter of 11 mm) flat-faced punches at a series of different compaction pressures between 3.5 MPa and 47 MPa, applied for 10 s.

Characterization of Tablets

Tablet crushing strength was measured in quintuplicate, registering the results as an average. For this purpose, it was used a tablet hardness tester Erweka TBH30. 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. The necessary pressure to eject the formed tablets was taken as the ejection pressure. For this purpose, hydraulic presses with a pointer for the maximal pressure reached were used. 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. The disintegration test is carried out using the disintegration tester and the procedure described in the Mexican Pharmacopeia (FEUM, 2004). The basket is immersed in a bath of water held at 37 ^{o}C, in a 1L beaker. The disintegration time was determined by triplicate, registering the results as an average. The test was carried out using tablets obtained at a low (6 MPa) and high (pressure needed to attain the maximal tablet hardness) compaction pressures.

Powder flow

The equipment used to assess the powder flow is similar to that used to determine the tap density of powders (Kibbe, 2000). Tapper was adjusted at a rate of 74 taps per minute and to elevate the graduated cylinder up to a height of 15 mm. This device uses a 100-ml graduated cylinder joined to a glass funnel with an orifice of 15 mm that can be closed with a glass rod. Once the sample is weighed and placed in the closed funnel, the device is started removing the glass rod at the same time. The time required to empty from the funnel 30 g of the powder, through the funnel orifice, is used to calculate the speed of the powder flow. The registered results are the average of 10 repetitions with the same sample. The powders were sieved through a mesh number 20 after each repetition.

RESULTS AND DISCUSsION

Compactibility

A pharmaceutical tablet has been described in physical terms as a large cluster of particles, held together by bonds active between external particle surfaces. The compactibility, defined as the capability of a material to form coherent agglomerates after compression, has been analyzed by studying the evolution of tablet tensile strength with increasing compaction pressure.The mechanical strength of a tablet provides a measure of the bonding potential of the material concerned and this information can be used as a functionality parameter in the selection of excipients.

Compactibility is associated with tablet hardness. Tablets must have sufficient mechanical strength to resist crumbling or breaking when being handled or processed, especially during packaging. Tablet hardness is therefore important and has practical relevance (Ilić*a et al.*, 2010).

In the case of lactose compactibility, the tensile strength has been observed to increase with an increasing compaction pressure up to a pressure of about 400 MPa. Thereafter, with increasing compaction pressure, the tablet tensile strength levelled out. The overall compactibility profile tended to be sigmoidal in shape (Fichtner *et al.*, 2008). Compactibility profiles with sigmoidal shape have been described with an equation based on the Weibull distribution (Castillo and Villafuerte, 1995a; Castillo and Villafuerte, 1995b). Recently, this model has been used to describe the compactibility of celluloses as indicative of their functionality as tablet excipients (Díaz and Villafuerte, 2010).

$$ln\ (-ln\ (1-D/dmax)) = n * ln\ Pc + I \quad \text{Eq. 1}$$

Where: *D* denotes the tablet's hardness or crushing strength, *Dmax* the maximal tablet hardness obtained, *Pc* the compaction pressure,

n the slope of the curve, and *I* the intercept of the curve.

The compactibility of the studied materials was defined using the regression parameters of eq. 1. The obtained compactibility curves describe the relationship between the hardness of the tablets and the compaction pressure used to obtain them. Figure 1 shows the experimental data and the calculated compactibility curves for Alfacel type 102 and its mixtures with amoxicillin, obtained after regression of experimental data. As can be seen, the data can be described properly with the applied model. The compactibility of binary mixtures of the above mentioned materials was studied to determine if the compactibility of the drug could be improved with the excipient and the magnitude of the improvement. In direct compression, it is necessary to use a dry binder to achieve the required tablet properties. In this way, Alfacel 102 was mixed with amoxicillin, as a dry binder. As observed in figure 1 Alfacel 102 improves the compactibility of amoxicillin at all ratios investigated.

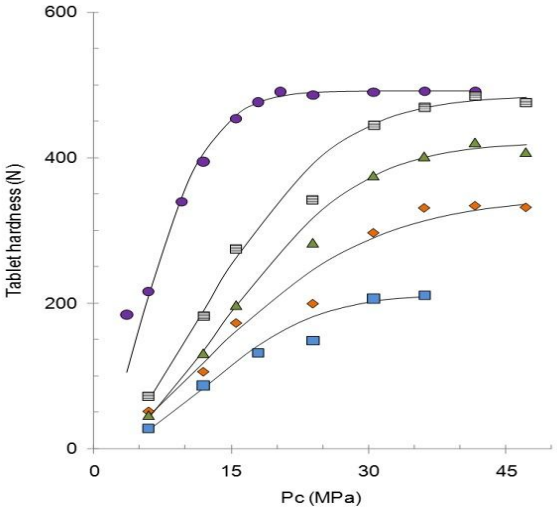

Fig. 1: Compactibility curves of mixtures of Alfacel type 102 and amoxicillin trihydrate determined with flat faced 500 mg tablets with diameter of 11 mm.

The tablet crushing strength of Alfacel 102, obtained at a compaction pressure of 36 MPa, was 491.6 N with a standard deviation, calculated from the 5 repetitions of individual points, of 7.9 N and a standard deviation, calculated from observed deviations of individual points from the regression line, of 18.6 N. It was followed by the mixtures of Alfacel 102 with amoxicillin (1:1; 50% Alfacel 102), displaying a tablet crushing strength of 468.3 N with a standard deviation from regression line of 18.6 N. The probability of the samples to be statistically not different is 1.3%. The differences in compactibility of the pure excipient and the mixtures with lower Alfacel 102 contents are greater and evident. Mixtures of amoxicillin containing 25% and 20% Alfacel 102 show tablet crushing strengths of 400.4±13.4 N and 310.7±18.9 N respectively. Finally, the tablet crushing strength of pure amoxicillin tablets was of 208.3±14.1 N. A comparison of the amoxicillin compactibility (Dmax) with that of the mixtures and Alfacel (Figure 2) shows a consistent increase of compactibility as the proportion of Alfacel 102 increases. This trend seems to approach a maximum in compactibility at about 35% Alfacel 102, with small change thereafter.

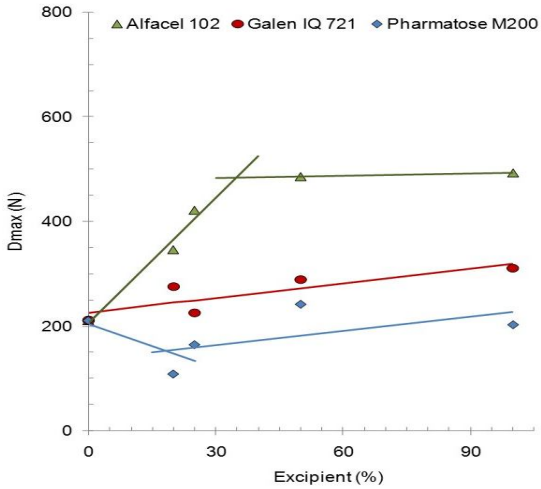

Fig. 2: Maximal tablet hardness (Dmax) attained by mixtures of amoxicillin trihydrate with different proportions of different excipients. 500 mg tablets with diameter of 11 mm.

The observed behavior of compactibility of mixtures of amoxicillin with microcrystalline cellulose has been observed before by mixtures of dicalcium phosphate with microcrystalline cellulose. The mixtures can be considered as a dispersion of a component in a continuous phase of the other one, changing the phases at the point of maximal tablet hardness (Castillo and Villafuerte, 1995a; Castillo and Villafuerte , 1995b; Garr and Rubinstein, 1991).

The explicit functionality of Alfacel 102, as a direct compression agglutinant, can be defined as the improvement of the drug compactibility obtained after addition of the excipient. Taking in account the mixtures with a continuous phase of the drug, first part of the curve on figure 2, Alfacel 102 increases the compactibility of amoxicillin in 7.9 N after addition of every unit of percentage of the excipient, until the maximum is attained. The surrogate functionality of pure Alfacel 102, expressed as the maximal tablet crushing strength of 500 mg circular flat faced tablets with 11 mm diameter is 492±18.6 N.

In the same way, it was observed the compaction behavior of mixtures of amoxicillin with Pharmatose M200. The compactibility of amoxicillin-Pharmatose mixtures decreases and then increases with an increasing content of Pharmatose M200. The minimum in tablet crushing strength was calculated at a Pharmatose M200 proportion of about 20-24%. A similar behavior has been observed by mixtures of lactose monohydrate with corn starch. It was observed a minimum in the relationship between the components proportion and the maximal tablet hardness reached by the mixtures. The tablet hardness was ruled by one component (continuous phase) and influenced by the second one (dispersed phase) in each one of the parts, before and after the minimum. The inflexion point was found at a corn starch proportion of about 31% (Villafuerte, 1990). One of the problems of lactose consists in its insufficient hardness when compressed,

due to the loose binding among the crystal particles, when used as an additive as crystallized in making tablets (Satomi and Imaoka, 2011). This is confirmed by the observed compactibility of amoxicillin formulations containing Pharmatose.

The maximal tablet hardness or crushing strength of Pharmatose M200 was 203 N with a standard deviation, calculated from observed deviations of individual points from the regression line, of 9.8 N. Mixtures of amoxicillin containing 25% and 20% Pharmatose M200 show tablet crushing strengths of 165±11.1 N and 110±7.9 N respectively. The maximal tablet crushing strength of pure amoxicillin tablets was of 208.3±14.1 N.

The compactibility of Pharmatose M200 is similar to that of amoxicillin. The results of an unpaired t-test show that the probability of this result, assuming the null hypothesis, is 0.29. In spite of that, the maximal tablet crushing strength of the mixtures are lesser and significantly different. Amoxicillin mixtures containing 20% and 25% Pharmatose M200, compared to pure amoxicillin, display results of an unpaired t-test showing that the probability of assuming the null hypothesis is less than 0.0001.

The explicit functionality of Pharmatose M200 is negative, decreasing the amoxicillin tablet crushing strength in -2.8 N after addition of every unit of percentage of the excipient, until the minimum is attained. The surrogate functionality of pure Pharmatose M200, expressed as the maximal tablet crushing strength of 500 mg circular flat faced tablets with 11 mm diameter is 203±9.8 N. The relative surrogate functionality of Pharmatose M200, taking as the unit of reference the surrogate functionality of Alfacel 102, is 0.41.

Although the explicit functionality of the excipients is faithful, it is referred to a single formulation and most probably is different for other formulations. In this sense, the surrogate functionality, although not explicit for a given formulation or process, is more useful as a general reference for different purposes, e. g. like quality control of raw materials. Moreover, it is indicative of the excipient's usefulness in tablets formulation. Another way to define the surrogate functionality of the excipient, not necessarily associated to an operational definition for tablets of a given weight, geometry and processing conditions, is the relative surrogate functionality; in this case taking as a reference the compactibility of microcrystalline cellulose type 102.

On the contrary, the mixtures of amoxicillin with GalenIQ 721 show neither a maximum nor a minimum in compactibility. The trend shows a linearly increasing compactibility as the proportion of GalenIQ 721 increases. From another point of view, GalenIQ 721 reduces linearly its compactibility as the proportion of amoxicillin increases. A similar reduction of compactibility of GalenIQ 721 when mixed with another substance has been observed before with 3% of the coarser grades of crospovidone. Addition of crospovidone led to a slight reduction in tablet mechanical strength of GalenIQ 721 (Babel and Fritzsching, 2009).The lower compactibility of GalenIQ compared to microcrystalline cellulose has been also observed before. About 15% lower compactibility of formulations with Galen IQ 721 was observed when compared to formulations containing dicalcium phosphate, Avicel PH 102 and their mixtures. This occurred by tablets of paroxetine.HCl hemihydrates containing 65-75% of the excipients (Yeole *et al*., 2010).

The maximal tablet crushing strength of GalenIQ 721 was 310 N with a standard deviation, calculated from observed deviations of individual points from the regression line, of 9.7 N. It was followed by the mixture of GalenIQ 721 with amoxicillin (1:1), 50% GalenIQ 721, displaying a maximal tablet crushing strength of 289 N with a standard deviation from regression line of 30.1 N. Mixtures of amoxicillin containing 25% and 20% GalenIQ 721 show tablet crushing strengths of 225±8.0 N and 275±16.7 N respectively. As above mentioned, the maximal tablet crushing strength of pure amoxicillin tablets was of 208.3±14.1 N.

The compactibility of GalenIQ 721 is higher than that of amoxicillin. The results of an unpaired t-test show that the probability of this result, assuming the null hypothesis, is less than 0.0001. Moreover, the maximal tablet crushing strength of the mixtures is greater and significantly different of that of amoxicillin. Amoxicillin mixtures containing 20% and 25% GalenIQ 721, compared to pure amoxicillin, display results of an unpaired t-test showing that the probability of assuming the null hypothesis is less than 0.0001 and 0.0074 respectively. In the case of mixtures with 50% GalenIQ 721 the probability of assuming the null hypotheses is also less than 0.0001.

The explicit functionality of GalenIQ 721 is positive, increasing the amoxicillin tablet crushing strength in 0.93 N after addition of every unit of percentage of the excipient, until the compactibility of GalenIQ 721 is attained. The surrogate functionality of pure GalenIQ 721, expressed as the maximal tablet crushing strength of 500 mg circular flat faced tablets with 11 mm diameter is 310±9.7 N. The relative surrogate functionality of GalenIQ 721, taking as the unit of reference the surrogate functionality of Alfacel 102, is 0.63. Compared to Pharmatose M200 (0.41), the relative compactibility of GalenIQ 721 is 1.5 times higher. If it is compared the explicit functionality of GalenIQ 721 (0.93 N/%) with that of Pharmatose M200 (-2.8 N/%) in formulations of amoxicillin, taking as a reference the explicit functionality of Alfacel 102 (7.9 N/%), can be obtained a relative explicit functionality parameter. GalenIQ 721 exhibited a relative explicit functionality, as a direct compression agglutinant, of 0.93/7.9 = 0.12. It means that GalenIQ will increase the compactibility of amoxicillin 12% of the increase obtained by the use of Alfacel type 102. After these determinations of compactibility it may possibly be obvious a lower functionality of GalenIQ and Pharmatose M200. However, it is noteworthy to say that the compactibility, as determined under the above mentioned conditions, is a parameter assessed with the aim to assign numerical values to a material's property and that the behavior of this material can be changed as the formula and process conditions change. The possible changes can reduce drastically the compactibility of Alfacel while maintaining that of GalenIQ 721 and Pharmtose M200. In this sense, it is generally accepted that lubricants like magnesium stearate has a more negative effect on the crushing strength of tablets constituted of deformable materials

(e.g. microcrystalline cellulose, Avicel) than brittle ones (e.g. $CaHPO_4$). Brittle materials are more likely to fracture and fragment during compaction. As more fresh surfaces, not covered by lubricant particles, are generated, they tend to bond together. Film formation on deformable particles, on the other hand, weakens the bonding of the granules as there are less fresh surfaces formed during compaction.

In the case of Magnesium stearate concentrations of 0.25, 0.5, 1.0 and 5% (w/w), there was a 6, 48, 63, and 86% decrease, respectively, in tablet crushing strength of Avicel 200 compacts at a compression pressure of 182 MPa. It has been further found that a magnesium stearate concentration of 0.4 markedly decreases the tensile strength of Avicel PH 102 tablets, and another marked decrease is observed with a concentration of 1.2% (Rashid *et al.*, 2010; Misiková, 2001).

The good compaction properties and low lubricant sensitivity of materials such as isomalt are maintained after agglomeration by fluid bed. This effect is caused by an early fragmentation of the agglomerated material during the compaction process, producing clean, lubricant-free particles and a high surface for bonding. Compaction profiles show that the direct compression forms of isomalt have sufficient compactibility and a low lubricant sensitivity (Bolhuis *et al.*, 2009a; Bolhuis *et al.*, 2009b). After all considerations and after the obtained results both compactibility parameters, the pure materials or surrogate functionality as well as the explicit or in a formulation functionality, show a superior compactibility of Alfacel 102 (492 N; 7.9 N/%) followed by GalenIQ 721 (310 N; 0.93 N/%) and thereafter by Pharmatose M200 (203 N; -2.8 N%). These results are summarized on table 1.

Table. 1: Compactibility as surrogate functionality SF-C, relative surrogate functionality RSF-C, explicit functionality with amoxicillin (EFA-C) and relative explicit functionality with amoxicillin (REFA-C).

Material	SF-C (N)	RSF-C	EFA-C (N/%)	REFA-C
Amoxicillin	208±14.1	0.42	-----	-----
Alfacel 102	492±18.6	1.0	7.9	1.0
GalenIQ 721	310±9.7	0.63	0.93	0.12
Pharmatose M200	203±9.8	0.41	-2.8	-0.35

SF-C - Calculated values ± standard deviation; EFA-C – N/unit percentage excipient in the mixture.

The mixtures of amoxicillin with the here studied excipients display all possible behaviors of compactibility: with a maximum, with a minimum or a straightforward linear relationship. The results are considered a consequence of the materials properties and the compaction conditions (magnitude and speed of the applied force).

A higher dispersion of the maximal tablet hardness data, corresponding to GalenIQ 721 and Pharmatose M200, observed in figure 2, is attributed to the absence of a lubricant. The compactibility curves and their regression parameters allowed the calculation of a response surface expressed as calculated compactibility curves for different mixtures of amoxicillin with Alfacel type 102. Figure 3 depicts the relationship between the tablet hardness, the proportion of Alfacel 102 in the mixture and the compaction pressure used to obtain the tablets.

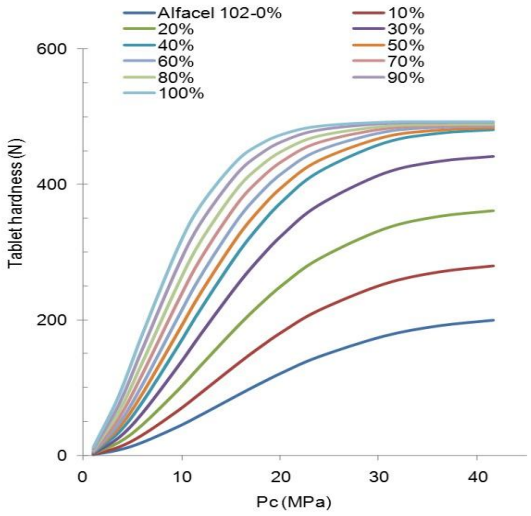

Fig. 3: Calculated compactibility curves for mixtures of amoxicillin trihydrate with different proportions of Alfacel type 102.

As can be seen, the lower proportions of Alfacel produce the more important increases in amoxicillin compactibility. Alfacel proportions up to 40% seem to be the more meaningful to be used when employing this excipient. Higher proportions of Alfacel produce less important increases in tablet hardness and because of that a less cost-efficient use of the excipient.

Likewise, the calculated response surface for the compactibility of mixtures of amoxicillin with GalenIQ 721 allowed the calculation of the compactibility curves depicted in figure 4. In this case the cost efficiency of the use of the excipient is equal at every proportion. This meaning that every increase of GalenIQ 721 in the mixture will improve the compactibility of amoxicillin in a similar magnitude, with the only limit of the own compactibility of the excipient.

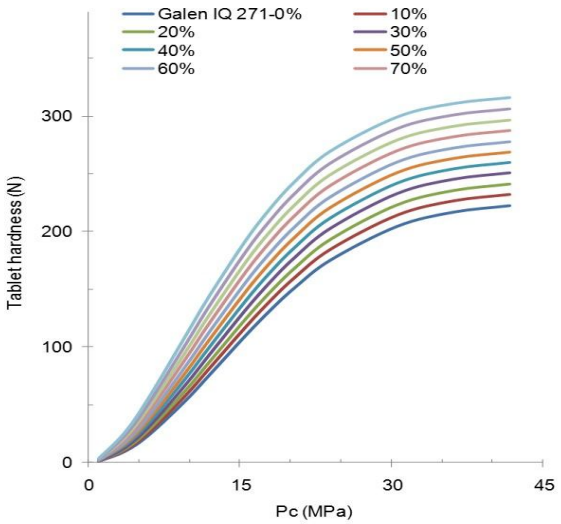

Fig. 4: Calculated compactibility curves for mixtures of amoxicillin trihydrate with different proportions of Galen IQ 271.

The calculated compactibility curves for mixtures of amoxicillin with Pharmatose M200 are depicted in figure 5. In this case and if the use of Pharmatose is necessary for any other reason different of compactibility; it is recommended the use of the smaller amount of the excipient in order to minimize its detrimental effect on the compactibility of amoxicillin.

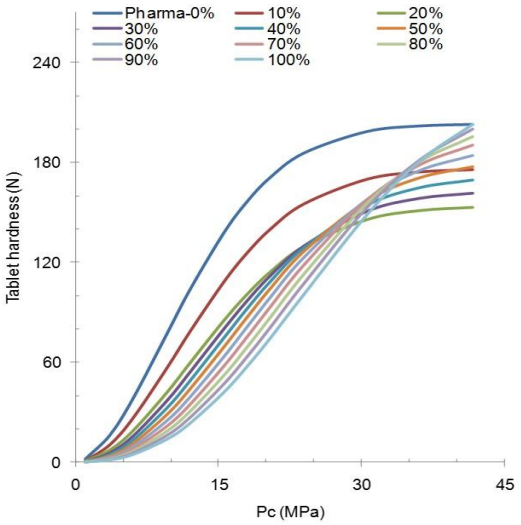

Fig. 5: Calculated compactibility curves for mixtures of amoxicillin trihydrate with different proportions of Pharmatose M200.

Ejection pressure

Apart of 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. Because of this, the ejection pressure can be considered a functionality parameter of excipients used in direct compression. In this way, the functionality of the excipients is related to a possible reduction of ejection pressure of tablets made of mixtures with a given drug or formula.

Pharmaceutical excipients that decrease friction at the interface between a tablet surface and the die wall during ejection reduce wear on punches and dies, prevent sticking to punch faces and improve manufacturing efficiency of solid preparations. Friction can also damage the machine and tablets during ejection (Ugurlu and Turkoglu, 2008).

The force or pressure necessary to eject a tablet involves the distinctive peak force required to initiate ejection by breaking the die-wall tablet adhesion. The second stage involves the force required to push the tablet up the die wall, and the last force is required for ejection of a tablet from the die (Patel *et al.*, 2007).

Microcrystalline cellulose tablets exhibit such a low coefficient of friction that they may need no lubricant. Microcrystalline cellulose has an extremely low coefficient of friction, both static and dynamic, so that it has no lubricant requirement itself (Swarbrick, 2004). This is attributed to the influence of its moisture content on the mechanical properties. It has been observed that the absorbed water might act as plasticizer and adsorbed water as lubricant (Bravo-Osuna *et al.*, 2007). Moisture can significantly reduce the force required to initiate ejection by the breaking of tablet/die-wall adhesions (Sáskaa *et al.*, 2010).

The ejection pressure obtained for tablets of microcrystalline cellulose, amoxicillin and their mixtures is depicted in Figure 6. As could be expected, Alfacel 102 tablets are easily released from the die they were compacted. Increasing compaction pressures and proportions of the drug in the mixtures increase drastically the ejection pressure. The experimental data were described with a logarithmic relationship.

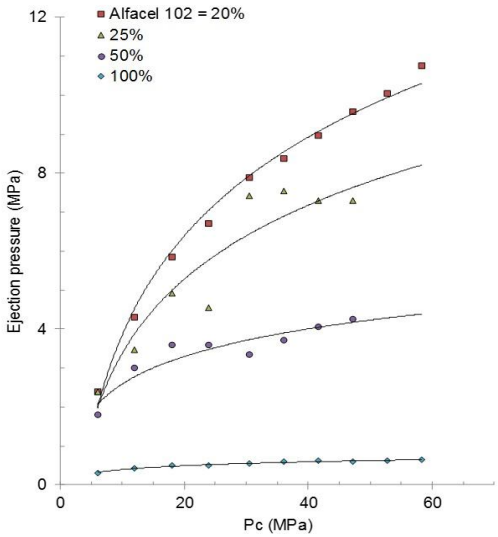

Fig. 5: Curves of ejection pressure of tablets made of mixtures of amoxicillin trihydrate with different proportions of Alfacel type 102. 500 mg tablets with diameter of 11 mm.

The lubricity of a material can be defined as freedom from friction or the property which diminishes friction. In this sense, lubricity is the measure of the reduction in friction. The lack of lubricity observed by amoxicillin can only be overcome with elevated Alfacel proportions.

Taking as a reference the logarithmic regression curves depicted in figure 6, it was calculated the pressure needed to release the tablets from the die when compacted at 40 MPa. Following the same procedure, the ejection pressure of tablets compacted at 40 MPa was calculated for the other two excipients and their mixtures. Figure 7 depicts the ejection pressure of tablets made of mixtures of amoxicillin trihydrate as function of different proportions of different excipients when compacted at 40 MPa.

Lubricity of a material cannot be directly measured, so tests are performed to quantify the material's performance. This is done here by determining the ejection pressure needed to release a tablet from a die, after a given compaction pressure was applied during a given amount of time. The greater the ejection pressures of the tablets the worse the lubricity.

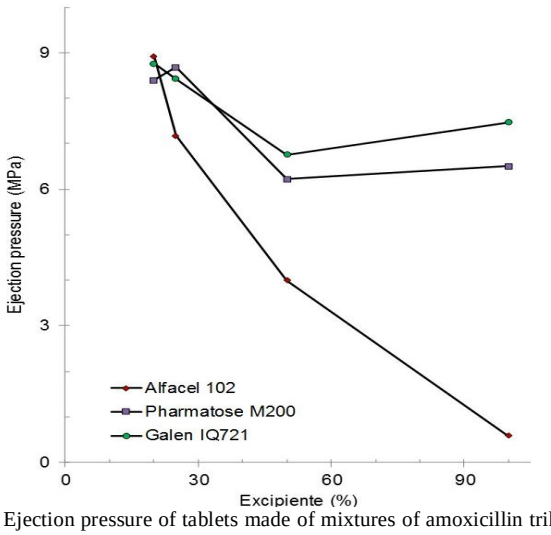

Fig. 7: Ejection pressure of tablets made of mixtures of amoxicillin trihydrate with different proportions of different excipients. Calculated for tablets obtained at Pc=40 MPa.

In a first approach, the ejection pressure of tablets of pure materials can be taken as a surrogate functionality of the material's lubricity or freedom of friction. Tablets of pure amoxicillin compacted at 40 MPa display a by regression calculated ejection pressure of 6.50±0.70 MPa. Alfacel 102 display an ejection pressure of 0.590±0.022 MPa, being the best lubricity of all here studied materials. In the same way, GalenIQ shows an ejection pressure of 6.446±0.954 MPa while Pharmatose M200 exhibit an ejection pressure of 6.506±0.451 MPa. The standard deviation was calculated from deviations of experimental data from the calculated ones. These data are summarized in Table 2.

Table. 2: Powder fluidity and tablet lubricity as surrogate functionality (SF-L) and relative surrogate functionality (RSF-L).

Material	SF-L (Pe-MPa)	RSF-L	Powder fluidity (g/s)
Amoxicillin	6.500±0.70	11.0	0.49
Alfacel 102	0.590±0.022	1.0	7.88
GalenIQ 721	6.446±0.954	10.9	14.4
Pharmatose M200	6.506±0.451	11.0	0.99

SF-L - Calculated values ± standard deviation; tablets compacted at 40 MPa.

The results of an unpaired t-test showed that the probability of assuming the null hypothesis when comparing amoxicillin, GalenIQ 721 and Pharmatose M200 is greater than 0.85. It means these materials have a similar ejection pressure and a poor lubricity compared to Alfacel 102. The probability of assuming the null hypothesis when comparing Alfacel 102 against amoxicillin is less than 0.0001.

In a second approach, a relative lubricity can be calculated by dividing the ejection pressure of the material's tablets by the ejection pressure of Alfacel 102. The calculated relative surrogate lubricity of amoxicillin is 11.0, for Pharmatose M200 and GalenIQ 721 are 11.0 and 10.9 respectively. It means that the necessary effort to release the tablets of amoxicillin, Pharmatose M200 and GalenIQ 721 is about 11 times that required to release tablets of Alfacel 102. The ejection pressure of amoxicillin tablets increases after the first addition of the different studied excipients (20%), declining thereafter. At low proportions of the excipients (20%) the ejection pressure of amoxicillin tablets is high (average of about 9.1 MPa); the predominant effect due to frictional properties of amoxicillin. A subsequent increase to 25% of the excipient's proportion showed a relative small decrease (6%) on the average ejection pressure of tablets obtained with Pharmatose M200 and GalenIQ 721. However, Alfacel 102 exhibits a reduction on the ejection pressure of about 21%. A further increase of the excipient's proportion to 50% reduced the ejection pressure of tablets obtained from mixtures of amoxicillin with Alfacel 102 in about 56% while by those obtained from mixtures with Pharmatose M200 and GalenIQ 721 the ejection pressure reduction was about 29%.

Alfacel data indicate a further reduction of ejection pressure as the Alfacel proportion increases while further increases in Pharmatose M200 and GalenIQ 721 indicate similar values of ejection pressure. The limit to reduce the ejection pressure of amoxicillin seems to be the own ejection pressure of the excipients. In this way, the functionality or capability of Alfacel to reduce the ejection pressure of amoxicillin will have a limit of 0.59 MPa while that of Pharmatose M200 and GalenIQ 721 have a limit of 6.48 MPa.

Pharmatose M200 and GalenIQ 721 exhibit a negative influence or dysfunctionality on the lubricity of amoxicillin although in the case of granulated mixtures of paracetamol and GalenIQ 801, the amount of applied excipient, isomalt, improved the lubricity of the granules (Sáskaa *et al.*, 2010). The improvement in lubricity is relative to what is taken as the reference. In the current case, an increase in lubricity can be observed by increasing the GalenIQ 721 proportion, taking as reference the ejection pressure of tablets containing 20% of the excipient.

Disintegration time

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. However, it can also be used as a functionality parameter for excipients used in direct compression tablets. For immediate release dosage forms it is preferred a rapid dissolution and in this sense, an excipient contributing to reduce the disintegration time can be considered as more functional.

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, heat of wetting and even dissolution of a fast dissolving material can be considered as a passive disintegration mechanism. 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. Alfacel can be considered a disintegrant with a mechanism of disintegration predominantly based on its water wicking properties. Pharmatose M200 and GalenIQ721 function mainly by a passive disintegration mechanism based on their high water solubility. Solubility of lactose in water is 18.9 g per 100 g solution at 25°C. About GalenIQ tablets disintegration, it is said that even without superdisintegrants tablets made with galenIQ™ 721 disintegrate very well. It shows a solubility of 42 g/100 g solution at 20 °C in water (GalenIQ 721, 2011).

Figure 8 shows the disintegration times obtained from tablets made of amoxicillin, different excipients and an average of tablets made of mixtures with different proportions of the excipients (20%, 25% and 50%) and amoxicillin. These tablets were compacted at low compaction pressure (6 MPa). Alfacel tablets display the highest disintegration time (6.68 min) mainly due to its higher compactibility, tablet hardness of 161.5 N. However, the disintegration time decreases to less than a minute (0.87 min) after being mixed with different proportions of amoxicillin. Tablets of pure amoxicillin show a lower disintegration time (0.38 min) and a lower compactibility, tablet hardness of 25.2 N. These disintegration results are consistent with observed tablet hardness results.

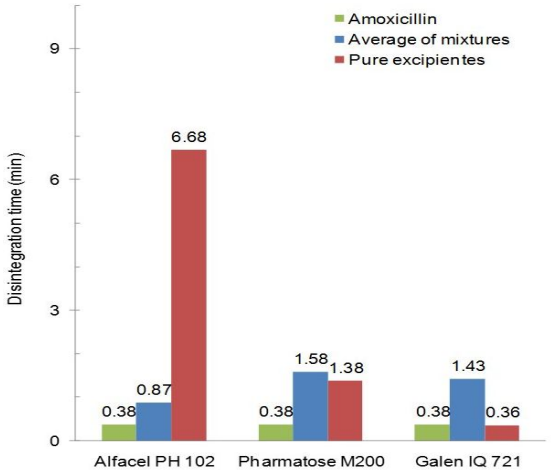

Fig. 8: Comparative disintegration time for tablets obtained at low compaction pressure and made of amoxicillin trihydrate, different excipients and an average of tablets made of mixtures of the drug and the excipients.

In view of the pure excipients, GalenIQ 721 tablets indeed display the lowest disintegration time (0.36 min), followed by Pharmatose M200 (1.38 min) and Alfacel 102 (6.68 min). In the same way, amoxicillin tablets exhibit a disintegration time of 0.38 min. However, considering that the disintegration time is relative to the tablet cohesiveness or mechanical strength, it can be considered as a surrogate functionality parameter the disintegrability of the tablets defined as the disintegration time divided by the crushing strength. Disintegrability expresses the time necessary to overcome every unit of tablet cohesiveness, the last one brought to light by the tablet crushing strength (determined in Newton). GalenIQ 721 exhibits the higher disintegrability and the lowest disintegration time, 0.33 s/N (0.36 min/64.7 N); followed by amoxicillin 0.90 s/N (0.38 min/25.2 N), Alfacel 2.48 s/N (6.68 min/161.5 N) and Pharmatose M200, with the lowest disintegrability or the higher time to overcome every unit of mechanical strength expressed in Newton, 4.47 s/N (1.38 min/18.5 N). The results are summarized on Table 3.

Table 3: Disintegrability, time to overcome every Newton of cohesiveness, as surrogate functionality (SF-D) and explicit functionality with amoxicillin (EFA-D).

Material	SF-D (s/N) Pc=6 MPa	EFA-D (s/N) Pc=6 MPa	EFA-D (s/N) Pc=MaxTCS
Amoxicillin	0.90	-----	-----
Alfacel 102	2.48	1.0	4.62
GalenIQ 721	0.33	3.39	6.34
Pharmatose M200	4.47	5.04	7.87

Tablets compacted at 6 MPa and at the pressure needed to attain the maximal tablet crushing strength, MaxTCS.

Considering as an explicit functionality parameter the increase in disintegrability or the reduction in disintegration time of amoxicillin tablets, in an average, the mixtures with Alfacel 102 display the higher disintegrability and the lower disintegration time, 1.0 s/N (0.87 min/52.2 N), followed by GalenIQ 721, 3.39 s/N (1.43 min/25.3 N) and Pharmatose M200 5.04 s/N (1.58 min/ 18.8 N). No one improves the pure amoxicillin tablets disintegrability (0.90 s/N).

The higher disintegrability (shorter disintegration time) of tablets containing mixtures with microcrystalline cellulose (Avicel PH 102), compared to GalenIQ 721, has been observed before by tablets of paroxetine.HCl including about 70% of these excipients and superdisintegrants, even if the presence of superdisintegrants is known to produce a less efficient functioning of passive or dissolving disintegrants and vice versa (López and Villafuerte, 2001).

Figure 9 displays the results obtained for the disintegration time of the above mentioned materials, obtained at high compaction pressure (compaction pressure needed to obtain the maximal tablet crushing strength). All excipients are capable to reduce the disintegration time of amoxicillin from more than 40 min to a range from 22 min to 32 min. Alfacel 102 mixtures display an average disintegrability of 4.62 s/N while the disintegrability of GalenIQ 721 mixtures is 6.34 s/N and that of Pharmatose M200 mixtures is 7.87 s/N.

Although the order in disintegrability of tablets obtained at high compaction pressures is the same as that observed by tablets compacted at 6 MPa, the disintegrability of the mixtures cannot be related straightforward to disintegrability of tablets obtained with pure materials. The surrogate functionality or functionality determined with pure materials for disintegrability showed a higher disintegrability or shorter disintegration time for GalenIQ 721, followed by Alfacel 102 and thereafter by Pharmatose M200. In both cases, surrogate and explicit functionality, Pharmatose M200 displays the higher disintegration times. However, the surrogate functionality for disintegrability of

GalenIQ is better than that of Alfacel 102 while the explicit functionality of the excipients with amoxicillin is the other way around.

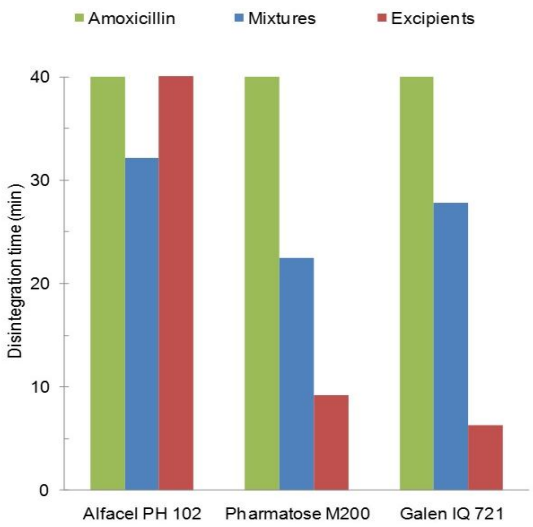

Fig. 9: Comparative disintegration time for tablets obtained at high compaction pressure and made of amoxicillin trihydrate, different excipients and an average of tablets made of mixtures of the drug and the excipients.

Powder flow

The fluidity of a powder can be defined intuitively as the easy of flow and relates to the change of mutual position of individual particles forming the powder bed. Powder properties, like those of any material, are a function of certain variables. They are influenced by a whole array of variables. Some are features of the particles themselves - size, shape, surface roughness, hardness, porosity, for instance - while others are connected with the system as a whole; air content, humidity and vibration being examples. Some powders, particularly those that are cohesive, retain air, as the particles tend to pack relatively inefficiently. Testing squeezes this air out making the sample progressively denser or stiffer and more resistant to flow. Another feature of cohesive powders is their propensity to agglomerate. As the primary particles move relative to one another cohesive forces bind them together, forming agglomerates. As with de-aeration this increases density, and flow energy raises correspondingly (Freeman, 2008).

Variables such as air and agglomerate content of powder samples are to be kept constant during testing. In this case this was made by sieving the sample after each repetition of the powder flow test.

Figure 10 depicts the powder flow of amoxicillin mixtures as a function of the excipient and excipient proportion. As can be seen, amoxicillin powder flow does not improve in an important manner by the admixture of the different excipients, at the excipients proportions studied. Although the three different excipients display quite different powder flow characteristics their effect on the drug powder flow is similar.

GalenIQ 721 is presented as a multifunctional excipient, known for its excellent compactibility, flowability and very low hygroscopicity. These and the combination of its other characteristics may make the filler-binder suitable especially for direct compression. As other especial bulk excipients Galen IQ 721 may possibly fulfill certain requirements such as dilution potential, flowability, content uniformity, physical and chemical stability, etc. Its large specific surface area could enable the incorporation of high concentrations of active ingredients without compromising the flow properties of the final mixture (Beneo Palatinit, 2010; Maj-Britt and Fritzsching, 2009).

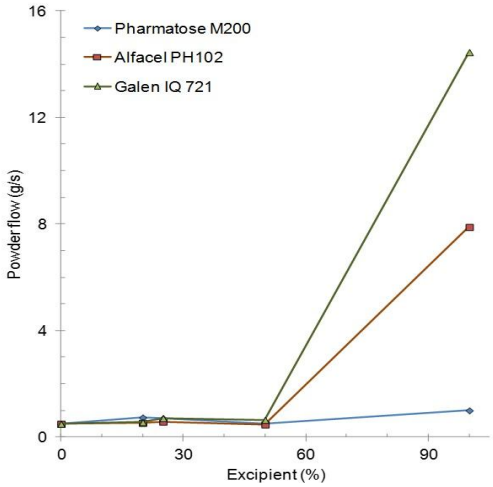

Fig. 10: Powder flow through a funnel with an opening of 15 mm of amoxicillin trihydrate, different excipients and mixtures of the drug and different proportions of the excipients.

As can be seen in figure 10 and according to its claimed properties GalenIQ 721 displays the better powder flow (14.4 g/s), followed by Alfacel (7.88 g/s) and Pharmatose M200 (0.99 g/s). These values can be considered as a surrogate functionality parameter for the excipients fluidity. In this sense, GalenIQ 721 can be considered the more functional excipient, compared to Alfacel 102 and Pharmatose M200. However, the better powder flow properties of GalenIQ 721 are not fully deployed to improve the poor powder flow of amoxicillin (0.49 g/s). The results are summarized on Table 2. The high dilution potential claimed for GalenIQ 721 can not be confirmed by the powder flow of mixtures with amoxicillin. An excipient proportion between 20% and 50% do not raise the flowability of amoxicillin as could be expected from flowability of the pure excipient. The same can be said for Alfacel, the flowability of the pure excipient is high enough to expect a higher improvement of the amoxicillin flowability. Pharmatose M200 seems to be consistent with its low flowability maintaining in the same magnitude the flowability of the drug.

A grade of microcrystalline cellulose (Avicel PH102) has been considered to lie near the borderline between acceptable and poor flow regions during high speed tableting. In this sense, it can serve as a reference material for judging adequacy of flow properties of prototype formulations. A powder exhibiting poorer flow properties than microcrystalline cellulose 102 (Avicel PH102) likely exhibits flow problems and should be avoided during formulation development to minimize potential flow problems during large scale tablet manufacture (Sun, 2010).

Moreover, the batch-to-batch flow functions of microcrystalline cellulose type 102 (Avicel PH 102) were found to be not statistically different at 95% confidence level, suggesting acceptable reproducibility. These results corroborate that microcrystalline cellulose type 102 may be used as a reference powder for predicting flow performance of a new formulation during high speed tableting (Shia, *et al.*, 2011).

Taking as a reference the powder flow of Alfacel 102, no one of the excipients can improve the flowability of amoxicillin to be processed in a high speed tableting machine. Although GalenIQ 721 as pure excipient displays much better flow properties than that of the reference, microcrystalline cellulose type 102, it does not have an important effect on the powder fluidity of the mixtures with amoxicillin. The functionality, understood as the excipients ability to improve the amoxicillin powder flow, is in all cases positive. However, considering the mixtures of different drug/excipient ratios as a whole (figure 11), the functionality of the excipients is small and far from the flowability of microcrystalline cellulose 102 (Alfacel 102) taken as a reference.

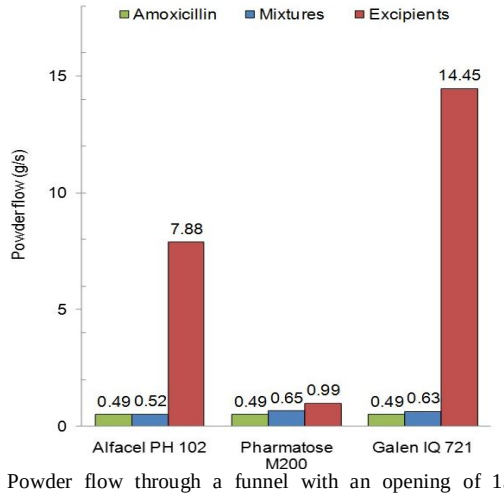

Fig. 11: Powder flow through a funnel with an opening of 15 mm of amoxicillin trihydrate, compared to different excipients and to an average of mixtures of the drug and different proportions of each excipient.

CONCLUSION

The role of the excipients is important in the composition of a tablet. They must ensure that the tableting operation (tabletability) can run satisfactorily and that tablets of good quality are prepared. The functionality of the excipients, to make better the above mentioned properties, can be determined to get a standard or to make a better selection of an excipient to improve the drug deficiencies. In this sense, surrogate functionality parameters, obtained with pure materials, can be used to get a standard with quality control purposes; to define the material´s properties and to measure and establish an acceptable variability of these properties. These parameters can include the surrogate and the relative surrogate functionalities for compactibility and lubricity of the powders and the surrogate functionality for disintegrability as well as the surrogate functionality for powder fluidity. The explicit functionality of a material applied to a given formula and/or process is more useful to predict the behavior of this material in a formula or process. However, it will be different, in most cases, when changing the formula and/or process limiting its usefulness. All the same, the determination of the explicit functionality in different formulas and process conditions can be used in dosage form development, as reference of a possible behavior to select formula components. In any case, it is desirable that every characteristic of the excipient is known, just to see if this characteristic contributes to better the process and tablet performance or at least do not contribute to worst them. The knowledge of other excipient properties, not known to give functionality to a given formulation, can be used to confirm or disprove selected excipients; e.g. excipients that improve a drug shortage but creates a new deficiency or a dysfunctionality.

Particularly, the surrogate functionality of GalenIQ 721 is better than Pharmatose M200; presenting a higher compactibility, powder fluidity and disintegrability but displaying similar lubricity. GalenIQ 721 exhibit lower compactibility and lubricity than Alfacel 102 but higher powder fluidity and disintegrability. The explicit functionality for direct compression of amoxicillin tablets of Alfacel 102 is superior to that of GalenIQ 721 and this one is better than that of Pharmatose M200. Although the GalenIQ 721 characteristics,predominantly brittle, are expected to be more stable to changes in formula composition and process conditions than those of Alfacel 102, plastic behavior.

REFERENCES

Babel, M. B., Fritzsching, B. Fast dissolving disintegrating tablets with isomalt. Pharm Tech. Eur. [on line]. 2009; 21 (2). Available at: http://pharmtech.findpharma.com/pharmtech/Ingredients/Fast-dissolving-disintegrating-tablets-with-isomal/ArticleStandard/Article/detail/577858. Accessed on 31 August, 2011.

BENEO-Palatinit presents its Multifunctional Excipient GalenIQ at AAPS 2010 [on line]. 2010. Press releases. Pharmaceutical Technology.com. Accessed on 14 September, 2011. Available at: http://www.pharmaceutical-technology.com/contractors/excipients/beneo-palatinit/press1.html.

Beneo Palatinit. GalenIQ 721 for direct compression. [on line]. Available at http://www.beneo-palatinit.com/Pdf/en/Pharma_Excipients/galenIQ/galenIQ_Grades/galenIQ721.pdf. Accessed on 31 August, 2011.

Bolhuis, G. K., Engelhart, J. J., Eissens, A. C. Compaction properties of isomalt. Eur J Pharm Biopharm. 2009a Aug;72(3):621-625. Epub 2009 Mar 25.

Bolhuis, G. K., Rexwinkel, E. G., Zuurman, K. Polyols as filler-binders for disintegrating tablets prepared by direct compaction. Drug Dev Ind Pharm. 2009b Jun; 35(6):671-677.

Bravo-Osuna, I., Ferrero, C., Jiménez-Castellanos, M. R. Influence of moisture content on the mechanical properties of methyl methacrylate–starch copolymers. European Journal of Pharmaceutics and Biopharmaceutics 2007;66(1):63-72.

Castillo, S., Villafuerte, L. Compactibility of binary mixtures of pharmaceutical powders. Eur. J. Pharm. Biopharm 1995a; 41(5):309-314.

Castillo, S., Villafuerte, L. Compactibility of ternary mixtures of pharmaceutical powders. Pharm. Acta Helv 1995b;70:329-337.

Çelik, M.,Okutgen, E. A Feasibility study for the Development of a Prospective Compaction Functionality test and the Establishment of a Compaction data bank. Drug Dev. Ind. Pharm 1993;19(17-18):2309-2334. (doi:10.3109/03639049309047193).

Chinta, D. D., Graves, R. A., Pamujula, S., Praetorius, N., Bostanian, L. A., Mandal, T. K. Spray-Dried Chitosan as a Direct

Compression Tableting Excipient. Drug Dev. Ind. Pharm. 2009;35(1):43-48. (doi:10.1080/03639040802149053)

Díaz Ramírez, C. C., Villafuerte Robles, L. Surrogate functionality of celluloses as tablet excipients. Drug Dev. Ind. Pharm 2010;36(12):1422-1435 (doi:10.3109/03639045.2010.487265).

DMV-Fonterra Excipients. Pharmatose®. Milled & sieved lactose. Product group overview [on line]. Available at http://www.dmv-fonterra-excipients.com/products/~/media/ DBF13799A281431 DB94DB5 C36CCC48B7.ashx. Accessed on 27 July, 2011.

Fichtner, F., Mahlin, D. Welch, K., Gaisford, S., Alderborn, G. Effect of Surface Energy on Powder Compactibility. Pharm. Res 2008;25(12):2750-2760. DOI: 10.1007/s11095-008-9639-7.

Freeman, R. Assessing powder stability [on line]. Freeman Technology; Jun 2008. Available at: http://www.freemantech.co.uk/es/descarga-de-documentos/articulos-y-libros-blancos.html#white-papers. Accessed on 05 October 2011.

Freeman, T. Implementing QbD: Powder characterization for design space definition. Freeman Technology [on line], September 2009. Available at: http://www.freemantech.co.uk/es/descarga-de-documentos/articulos-y-libros-blancos.html. Accessed on 02 August, 2011.

GalenIQ 721. DC grade for fast disintegrating tablets [on line]. Available at: http://.higuchi-inc.co.jp/pharma/excipient/isomalt/pdf/detail_galenIQ721.pdf. Accessed on September 12, 2011.

Garr, J. S. M., Rubinstein, M. H. The effect of rate of force application on the properties of microcrystalline cellulose and dicalcium phosphate mixtures. Int. J. Pharm 1991;73:75-80.

Hancock, B. C. Achieving a Perfect Tablet Formulation: Evolution, or Intelligent Design? Am. Pharm. Rev. [on line] March, 2009. Available at: http://americanpharmaceuticalreview.com/ViewArticle.aspx?ContentID=3969. Accessed on 31 July, 2009.

Ilića, I., Kása, P., Dreua, R., Pintye-Hódib, K., Srčiča, S. A modification of the Pr value equation for measuring the compactibility of pharmaceutical materials. Chemical Engineering and Processing: Process Intensification 2010;49(8):881-884.

Kibbe, A. H. Editor. Handbook of pharmaceutical excipients, third edition, London: Pharmaceutical Press, 2000:641.

López Solís y L. Villafuerte Robles. Effect of disintegrants with different hygroscopicity on dissolution of norfloxacin/Pharmatose DCL 11 tablets. Int. J. Pharm 2001; 216(1-2):127-135.

Maj-Britt, B., Fritzsching, B. Fast dissolving disintegrating tablets with isomalt. Pharmaceutical Technology Europe, 2009; 21 (2) [on line]. Accessed on 14 September, 2011. Available at: http://pharmtech.findpharma.com/pharmtech/article/articleDetail.jsp?id=577858&pageID=1&sk=&date=.

Moreton. R. Ch. Functionality and Performance of Excipients. Pharm. Tech. [on line], October 1, 2006. Available at: http://pharmtech.findpharma.com/pharmtech/Excipients/Functionalityand-Performance-of-Excipients/ArticleStandard/Article/detail/378395. Accessed on 25 March, 2010.

Muzíková J. The firmness of Avicel PH 102 and Avicel PH 301 compression and the effect of magnesium stearate.Ceska Slov Farm. 2001 Mar;50(2):92-94.

Muzíková, J., Pavlasová, V. Energy evaluation of the compaction process of directly compressible isomalt. Ceska Slov. Farm 2011;60(1):11-6.

NB's Sancel. Microcrystalline cellulose I. P. The excipient of choice [on line]. Available at http://www.nbent.com/details.htm. Accessed on 31 August, 2011.

Nokhodchi, A., Rubinstein, M. H., Larhrib, H., Guyot, J. C. The effect of moisture content on the energies involved in the compaction of ibuprofen. Int. J. Pharm 1995;120(1):13-20.

Olmo, I. G., Ghaly, E. S. Evaluation of Two Dextrose-Based Directly Compressible Excipients. Drug Dev. Ind. Pharm1998;24(8):771-778. (doi:10.3109/03639049809082725).

Patel, S., Kaushal, A. M., Bansal, A. K. Lubrication Potential of Magnesium Stearate Studied on Instrumented Rotary Tablet Press. AAPS PharmSciTech. 2007;8(4): Article 89. Available at http://www.aapspharmscitech.org/articles/pt0804/pt0804089/pt0804089.pdf. Accessed on 09 October, 2009.

Patel, A. Multifunctional excipients creating new possibilities. Contrac Pharma [on line], November/December, 2009. Accessed on 26 April, 2010. Available at: http://www.contractpharma.com/issues/2009-11/view_features/multifunctional-excipients/.

Rashid, I., Daraghmeh, N., Al-Remawi, M., Leharne, S. A., Chowdhry, B. Z., Badwan, A. Characterization of the impact of magnesium stearate lubrication on the tableting properties of chitin-Mg silicate as a superdisintegrating binder when compared to Avicel® 200. Powder Technology 2010;203:609–619.

Sáskaa, Zs., Dredána, J., Balogha, E., Luhnb, O., Shafira, G., Antala, I. Effect of isomalt as novel binding agent on compressibility of poorly compactable paracetamol evaluated by factorial design. Powder Technology 2010;201(2):123-129.

Satomi, J., Imaoka,M. Excipient for compressed tablets comprising novel spherical mannitol. US patent, US 2011/0135927 A1, Pub. Date Jun. 9, 2011.

Schmidt, P. C., Rubensdörfer, C. J. W. Evaluation of Ludipress as a "Multipurpose Excipient" for Direct Compression: Part I: Powder Characteristics and Tableting Properties. Drug Dev. Ind. Pharm 1994;20(18):2899-2925. (doi:10.3109/03639049409042687).

Shia, L., Chattoraja, S., Sun, Ch. C. Reproducibility of flow properties of microcrystallinecellulose-Avicel PH102. Powder Technology 2011; 212(1):253-257.

Sun, Ch. C. Setting the bar for powder flow properties in successful high speed tableting. Powder Technology 2010; 201(1):106-108.

Swarbrick, J. Encyclopedia of pharmaceutical technology. Update Supplement. Informa HealthCare; 2nd edition, 2004:3680-3681.

Traini, D., Young, P. M., Jones, M., Edge, S., Price, R. Comparative study of erythritol and lactose monohydrate as carriers for inhalation: Atomic force microscopy and in vitro correlation. Eur. J. Pharm Sci 2006;27:243–251.

Ugurlu, T., Turkoglu, M. Hexagonal boron nitride as a tablet lubricant and a comparison with conventional lubricants. International Journal of Pharmaceutics 2008;353(1-2):45-51.

Villafuerte Robles, L. Compactabilidad de tabletas de una mezcla de dos componentes: almidón de maíz-lactosa. Rev.Mex. C. Farm. 1990;21(3):20-27.

Villafuerte L. The excipients and their functionality in pharmaceutical solid products. Rev. Mex. C. Farm 2011;42(1):18-36.

Yeole, Ch. N., Darekar, S. S., Gupta, A., Shrinivasan, G. Formulation and Evaluation of Immediate Release Tablet of Paroxetine Hydrochloride. Journal of Pharmacy Research 2010;3(8):1736-1738.

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