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Polysaccharide Absorbents in Moisture Activated Dry Granulation

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Abstract

The aim of the present work was to study the hydrogel-forming polysaccharides carrageenan, guar and xanthan gum as potential absorbents in moisture activated dry granulation (MADG). Preferences of formulators regarding absorbents tend to incline towards microcrystalline cellulose and colloidal silicon dioxide. Besides, only few works exploring modified drug release achieved by MADG are reported in literature. A factorial design of experiments was introduced to study the effect of formulation variables on granulates and their tablets. Contact angle and drop penetration time provided useful information for guidance on excipient selection. Metronidazole was used as a highly soluble model drug to verify the release performance achieved with the polysaccharides. All of the granulates yielded tablets with appropriate physical properties, and significantly different disintegration behaviors and drug release profiles. Absorbent, binder and their mutual interaction had significant effects on formulation performance. The type of absorbent affected tablet disintegration time and drug release. The presence of copovidone, alone or in combination with povidone, proved to be a good choice for granulating a high load of not directly compressible materials by MADG. Carrageenan, guar and xanthan gum should be regarded as promising moisture absorbents for either immediate or extended release tablet formulations produced by MADG, an energy and time efficient granulation process. A broader range of absorbents could provide more versatility in MADG formulation and this advantageous process become more eligible for producing modified release products.

Keywords: Moisture activated dry granulation; Polysaccharides; Absorbents; Wettability; Modified drug release

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Abbreviations

MADG: Moisture Activated Dry Granulation; QbD: Quality by Design; DoE: Design of Experiments; ANOVA: Analysis of Variance; PCA: Principal Component Analysis; CA: Cluster Analysis

Introduction

The aim of the present work was to study hydrogel-forming polysaccharides as potential absorbents in moisture activated dry granulation (MADG). MADG is an attractive granulation process. It offers advantages regarding energy saving, time efficiency, suitability for continuous processing [1] and formulation versatility, including polymeric matrix type controlled release products [2,3]. However, only few works exploring modified drug release achieved by MADG are reported in literature [2,4,5]. MADG also presents fewer critical process variables than conventional wet and dry granulation processes, a relevant characteristic which facilitates the implementation of quality by design (QbD) [6], as well as process scale up and validation.

Briefly, in MADG, a small amount of water is used to activate agglomeration within a powder mixture, followed by the addition and blending of ingredients that absorb and distribute the moisture, thus not requiring heat to dry the granules. The result is a uniform, free-flowing, and compactible granulation [7]. MADG process requires nonabsorbent, easy-to-wet fillers [7]. Regarding binders, Ullah et al. [7] reported that they should be easily wettable and become tacky with the addition of a small amount of water. The author and his co-workers considered that low-viscosity polyvinylpyrrolidones were ideal for this purpose. However, they also pointed out that binders with very low viscosity may not provide enough tackiness for agglomeration. The required balance between distribution ability and agglomeration efficiency of binders may not always be easy to accomplish using only one binder agent in the process. The use of combinations of binders could

Table 1: 3^2 factorial experimental design: factors and responses.

Factors	Levels		
	Low	Medium	High
X_1: type of first absorbent	Guar gum	k-Carrageenan	Xanthan gum
X_2: type of binder	Povidone	Copovidone	Povidone/Copovidone
Responses			
Y_1: 50th percentile (Perc50)		Y_6: moisture content (Moist)	
Y_2: span (span)		Y_7: disintegration time (Desinteg)	
Y_3: apparent density (DensApar)		Y_8: friability (FriabCM)	
Y_4: tapped density (DensAsent)		Y_9: tensile strength (Ftensil)	
Y_5: compressibility index (IC)		Y_{10}: RSD of tablet weight (RSD)	

widen opportunities to improve granulation performance. Excipients such as microcrystalline cellulose [2,4,7-11], colloidal silicon dioxide [7,8,10-12], pregelatinized corn starch [10,13], magnesium aluminometasilicate [10], potato starch [14], maltodextrins [1] and some of their combinations have been described in the literature as absorbents used to distribute the moisture present in the granulates. According to literature, preferences of formulators tend to incline towards microcrystalline cellulose and colloidal silicon dioxide. Some authors even refer to MADG as a granulating method that requires microcrystalline cellulose to absorb moisture [4]. More than 70% of any MADG formulation is agglomerated, and the remaining portion of excipients - consisting of moisture absorbents, disintegrants and lubricants - is added as is. Therefore, it is desirable that nonagglomerated excipients are closer in particle size distribution to the agglomerated portion of the formulation to minimize the potential for segregation [7]. Microcrystalline cellulose is available in comparable particle sizes, thus favoring its selection as moisture absorbent. Currently, several hydrogel-forming polymers are widely used in controlled drug delivery systems. Natural occurring polysaccharides are among the hydrogel-forming polymers selected for release retardation in the gastrointestinal tract, for example, in colonic release [15-17] or gastric floating systems [18-20]. They are considered advantageous in comparison to synthetic polymers in the formulation of hydrogels. These biocompatible polymers are widely present in living organisms, thus, available from renewable sources, cultures of microbial selected strains, as well as through recombinant DNA techniques [16]. However, the ability to absorb large quantities of water of hydrogel-forming polymers could interfere with MADG granule formation mechanism if such excipients were incorporated as matrix fillers in the agglomerated portion of formulations. Besides, when considered for incorporation in the non agglomerated portion, two other characteristics are disadvantageous: their limited compressibility properties [21-23], and their medium particle sizes which are in general, smaller than MADG granules. Nevertheless, hydrogel-forming polysaccharides arise as potential moisture absorbents in MADG, which could lead to tablets able to display different disintegration behaviors and drug release profiles. In the present work, in addition to the widely used microcrystalline cellulose, polysaccharides such as k-carrageenan, guar gum and xanthan gum were selected as absorbents. k-Carrageenan is an

Table 2: Formulations of placebo tablets as per the 3^2 factorial experimental design.

Component	Run N°								
	1	2	3	4	5	6	7	8	9
	% w/w								
Lactose monohydrate	37.80	37.80	37.80	37.80	37.80	37.80	37.80	37.80	37.80
Calcium phosphate dihydrate	37.80	37.80	37.80	37.80	37.80	37.80	37.80	37.80	37.80
Povidone K15	7.86	7.86	-	1.97	-	-	1.97	7.86	1.97
Copovidone	-	-	7.86	5.90	7.86	7.86	5.90	-	5.90
Deionized water	2.95	2.95	2.95	2.95	2.95	2.95	2.95	2.95	2.95
Guar gum	7.37	-	-	7.37	-	7.37	-	-	-
k-Carrageenan	-	7.37	-	-	7.37	-	7.37	-	-
Xanthan gum	-	-	7.37	-	-	-	-	7.37	7.37
Microcrystalline cellulose	4.42	4.42	4.42	4.42	4.42	4.42	4.42	4.42	4.42
Amorphous silica	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
Magnesium stearate	0.75	0.75	0.75	0.75	0.75	0.75	0.75	0.75	0.75

Table 3: Result data of mean values of responses used in PCA.

Run No	Perc50 (um)	span	DensApar (g/mL)	DensAsent (g/mL)	IC (%)	Desinteg (min)	FriabCM (%)	Ftensil (MPa)
1	145.3	3.6	0.52	0.68	23	6	0.0	2.3
2	141.5	3.6	0.47	0.61	22	40	0.0	1.6
3	106.0	2.6	0.60	0.68	11	213	0.2	2.3
4	124.4	2.5	0.57	0.71	19	5	0.5	1.9
5	109.4	3.0	0.59	0.64	8	58	0.1	1.8
6	105.2	3.1	0.63	0.75	15	4	0.2	2.4
7	106.0	2.7	0.57	0.70	20	47	0.2	1.4
8	118.9	3.4	0.53	0.64	17	149	0.1	1.6
9	101.4	2.8	0.58	0.77	25	154	0.2	1.9

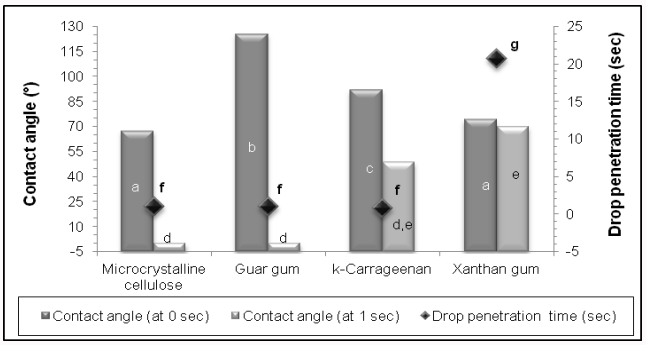

Figure 1: Contact angles (°) at time 0 sec and 1sec, and drop penetration times (seconds) of moisture absorbents. Different superscripts within a property imply significant differences ($p<0.05$) when absorbent sample was taken as source of variation. Superscripts denoting significant differences per property: a, b, c for contact angle at 0 sec; *d, e* for contact angle at 1 sec; ***f,g*** for drop penetration time.

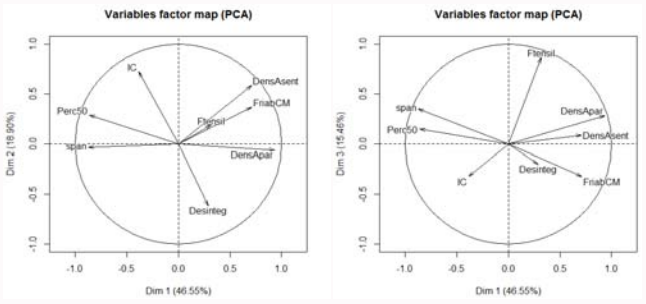

Figure 2: Representation of the variables in the PCA: a) first and second dimensions; b) first and third dimensions.

anionic polymer isolated from marine red algae. Guar gum is non-ionic and commercially isolated from the seeds of several leguminous plants, while xanthan gum is an anionic polysaccharide commercially obtained by bacterial fermentation [24]. With respect to compactability, carrageenan and xanthan gum form tablets by plastic deformation, but elastic recovery is high, thus, less energy is transformed into pure plastic deformation [25,26]. Guar gum also exhibits poor flowability and compressibility [27].

Metronidazole, a nitroimidazole classified as antiamoebic, antigiardiasis and antibacterial agent, was used as a highly soluble model drug to verify the release performance achieved with the studied hydrogel-forming polysaccharides. The WHO Essential Medicines List includes metronidazole tablets with strengths ranging from 200 to 500 mg [28].

This paper summarizes the results obtained in the present study intended to draw attention to the use of hydrogel-forming polysaccharides as versatile absorbents, able to aid in modulating drug release in an energy and time efficient granulation process such as MADG.

Materials and Methods

Materials

The excipients used in the present work were as follows: fine grade lactose monohydrate (Pharmatose 200M (NZ), DFE Pharma), calcium hydrogen phosphate dehydrate (Emprove extra fine, Merck), povidone K15 (PVP K15, ISP), copovidone (Kollidon VA 64, Basf), guar gum (guar gum powder, BdV Behrens), xanthan gum (xanthan gum, Weifang Ouchem), microcrystalline cellulose (Vivapur 102, JRS) and amorphous silica (Syloid 244FP, Grace). Potassium salt kappa carrageenan (Gelcarin GP812 NF) was kindly gifted by FMC Corporation. Magnesium stearate was locally purchased. The active ingredient was metronidazole (Hubei Hongyuan Pharmaceutical Technology).

Preparation of granulates and tablets

Experimental design: A 3^2 factorial design of experiments (DoE) was introduced to study the effect of formulation variables on granulates obtained by MADG and their tablets. The effects of type of moisture absorbing material on quality attributes of the products were investigated in presence of different binders. Granulate attributes such as particle size distribution, bulk density and compressibility index, as well as tablet attributes such as weight uniformity, disintegration time and mechanical strength, were evaluated. The investigated factors along with their levels and the corresponding responses are summarized in Table 1. A design matrix comprising 9 experimental runs was constructed using quality Tools package [29], R language [30]. The compositions of all of the runs are given in Table 2. The amounts of the formulation components were determined in preliminary studies.

After the DoE, the most promising formulations were used to produce metronidazole tablets in order to verify different release profiles achieved by the hydrogel-forming moisture absorbents.

Manufacturing process: Batches of 1000g were processed in a high speed mixer granulator (MG 3VS-BSP, PMS, Thailand) equipped with a 3L granulation bowl. All solid materials were previously sifted through a 0.4mm screen. Filler (or filler plus active ingredient, in metronidazole tablets) was initially blended with the binder in the granulation bowl. Immediately, the powder blend was granulated by

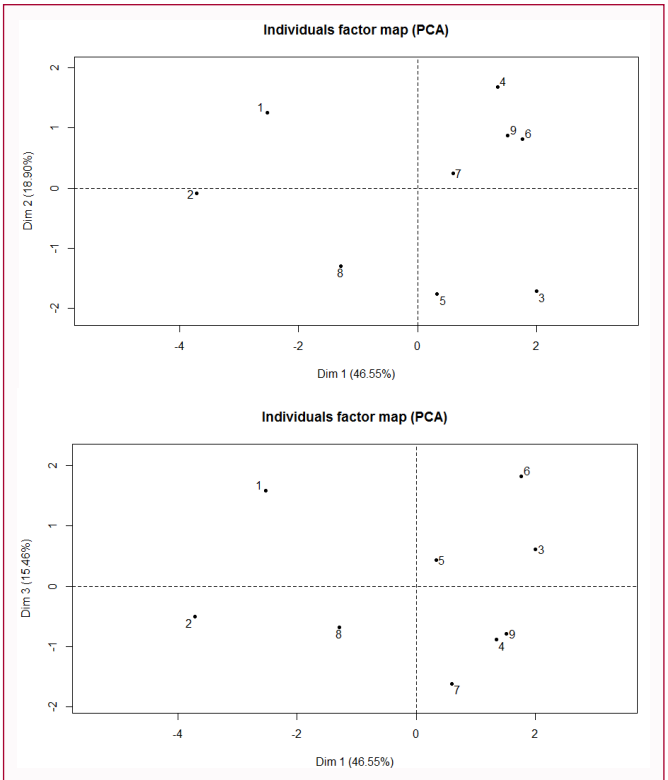

Figure 3: Representation of the runs in the PCA: a) first and second dimensions; b) first and third dimensions.

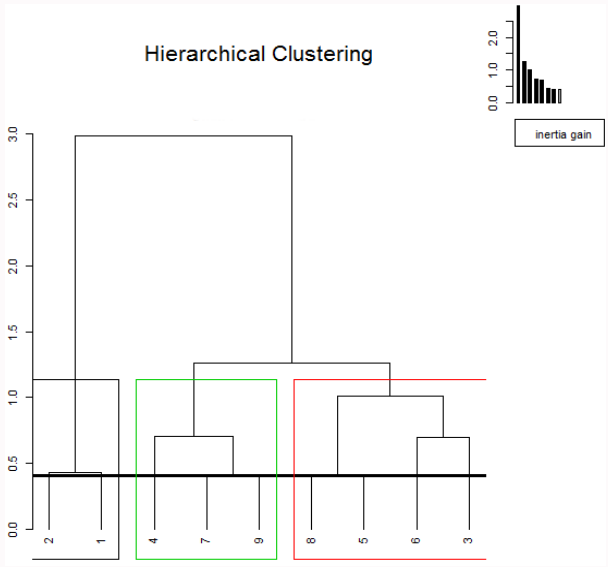

Figure 4: CA dendrogram.

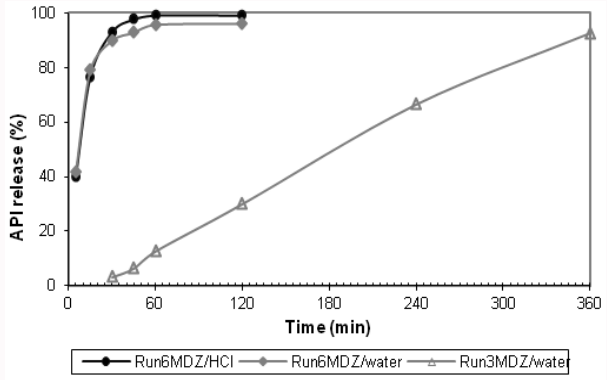

Figure 5: Metronidazole release profiles in hydrochloric acid (HCl, USP apparatus 1) and in water (USP apparatus 2).

spraying water for 10s (flat fan spray pattern) at 380 rpm impeller speed and 1200rpm chopper speed for 2min. For the 2min absorption stage, the first moisture absorbent (carrageenan, guar gum or xanthan gum) was added followed by the second absorbent (microcrystalline cellulose) at 380rpm impeller speed. Granulate was screened through a 0.7mm screen. Granulate plus silica was mixed for 5 minutes in a tumbling mixer (Turbula, Willy A. Bachofen, Muttenz, Switzerland). At the end of the mixing time, magnesium stearate was added to the turbula and mixed for another 3 minutes. Finally, each blend was compacted into tablets in a rotary tablet press (RL15, Kilian, Germany) at 20kN, using 8mm concave round tooling.

According to Ullah [3], ingredients should be added in a specific order in MADG formulations. In the present work, each hydrogel-forming polysaccharide was added first, in order to absorb most of the water, followed by microcrystalline cellulose, further absorbing any remaining moisture.

Evaluation of materials

Characterization of excipients: Wettability has been pointed out as a relevant characteristic to assess on MADG absorbents [10]. Takasaki et al. [10] concluded that among the excipients they studied, powder wettability of moisture absorbents was a key driver for rapid disintegration of tablets. In a previous work [13], similar results were found, but as expected, also binder characteristics impacted on disintegration time.

Contact angle and drop penetration time of moisture absorbents were measured from recorded films of a single drop of water penetrating into the powder surface, as reported in a previous work [13]. At least 3 replicates were performed on each dish of powder.

Characterization of granulates: Particle size distribution, bulk density and compressibility index were determined based on United States Pharmacopeia (USP). Particle size distributions were determined by sieve analysis (AS 200 control, Retsch, Haan, Germany). DIN-ISO 3310/1 standard sieve series was 75, 90, 125, 180, 250, 355 and 500 um. The 10th, 50th and 90th percentiles (Perc10, Perc50 and Perc90, respectively), and span were calculated. The following formula was used to calculate span: (Perc90 - Perc10)/ Perc50. The moisture content was determined on a halogen moisture analyzer (Mettler Toledo HR 73, USA) and the percentage of moisture content was calculated from the weight loss of the sample on heating.

Characterization of tablets: Appearance and dimensions, weight uniformity, hardness, friability and disintegration time of tablets were studied. Friability and disintegration time were determined according to the USP. Hardness and diameter were measured with a hardness tester (TBH 125, Erweka, Heusenstamm, Germany) and a caliber, respectively. The results were used to calculate tensile strength by the following formula[31]: $10H/(\pi D^2)[(2.84T/D) - (0.126T/t) + (3.15t/D)+0.01]^{-1}$; where H is hardness, D is diameter, T is overall thickness and t is central cylinder thickness. In vitro drug release from metronidazole tablets was performed according to USP <711>. Either dissolution apparatus 1 or 2 at 100 rpm or 50 rpm, respectively, were used in a dissolution tester (VK 7000 10-1700, Vankel, USA).

Average results were reported for all of the tests. Characterization of granulates and tablets was performed 4 days after manufacturing.

Data analysis

Two-way analysis of variance (ANOVA), principal component analysis (PCA) and cluster analysis (CA) were used for data analysis of granulates and tablets. One-way ANOVA was performed on contact angle and drop penetration time of excipients, considering run as fixed source of variation. Honestly, significant differences for a significance level of 0.05 were calculated using Tukey's test in both ANOVAs. Nine samples and eight variables were taken into account to perform PCA. The variables included were as follows: Perc 50, span, Dens Apar, Dens Asent, IC, Desinteg, Friab CM and Ftensil. These granulate and tablet properties (Y responses) for all of the experimental runs are given in Table 3. Cluster analysis was performed after PCA to identify groups of products with different characteristics, considering Euclidean distances and Ward's aggregation criterion.

All data analyses were performed using R language [30] and Facto Mine R package [32].

Results and Discussion

Characterization of excipients

Contact angle and drop penetration time of moisture absorbents are presented in Figure 1. These parameters showed xanthan gum was the least wettable absorbent of the four used in the present work. Xanthan gum presented a promising low initial contact angle, similar to microcrystalline cellulose. However after 1sec, this angle remained

Table 4: Formulations of metronidazole tablets.

Component	Formulation	
	Run6MDZ	Run3MDZ
	% w/w	
Metronidazole	60.61	60.61
Lactose monohydrate	7.52	7.52
Calcium phosphate dihydrate	7.52	7.52
Copovidone	7.86	7.86
Deionized water	2.95	2.95
Guar gum	7.37	-
Xanthan gum	-	7.37
Microcrystalline cellulose	4.42	4.42
Amorphous silica	1.00	1.00
Magnesium stearate	0.75	0.75

persistently high, and its drop penetration time was the longest of the selected absorbents. Guar gum showed an opposite behavior. Initially, it presented the highest contact angle, but it decreased sharply to 0° after 1sec, similarly to microcrystalline cellulose. No significant differences in contact angle after 1sec or in drop penetration time were found between guar gum, carrageenan and microcrystalline cellulose. Moreover, their drop penetration times were sufficiently short, thus, a similar proper wetting behavior was expectable for the three absorbents [33].

Characterization of granulates and tablets

Factorial experimental design: The MADG granulates presented compressibility index values which ranged from passable (25%) to excellent flow character (8%) [34], as it is shown in Table 3. Moisture content of granulates ranged between 3.7 and 4.9% after absorbent was used to redistribute moisture within each batch, producing relatively dry beds for adequate compaction. Tablets with appropriate aspect and mechanical strength (tensile strength values between 1.4 and 2.4 MPa [31], and friability weight loss below 0.5%) were obtained from these granulates. The results of relative standard deviation of tablet weight were below 2%, excepting run 4 (6.5%). Tablet disintegration time ranged from 4min to more than 3 hours. Therefore, this attribute appeared as the most distinctive tablet property for comparison purposes among experimental runs.

The first three dimensions of the PCA explained 81% of the variance of the experimental data. As depicted in Figure 2, the first principal component (Dim1) was responsible for 47% of the total variance in the data set, the second (Dim2) was responsible for 19% and the third for a further 16% (Dim3). The first dimension is positively correlated to Dens Ap, Dens Asent and Friab CM, while negatively correlated to Perc50 and span. The second dimension is positively correlated to IC, while negatively correlated to Desinteg. Finally, the third dimension is positively correlated to Ftensil.

PCA revealed the following trends. Moisture absorbents mainly influenced tablet disintegration time. The type of absorbent made disintegration time vary from 4 to 6 min in presence of guar gum (runs 1, 4 and 6, high values in Dim2 in Figure 3a) to more than 2 hours in xanthan gum-containing formulations (low values in Dim2 in Figure 3a). Therefore, the less wettable the absorbent present in the formulation, the higher is tablet disintegration time. k-Carrageenan (runs 2, 5 and 7), produced tablets showing intermediate disintegration time values (between 40 and 58 min).

Table 5: Result data of mean values of properties of metronidazole tablets.

Run	Desintegration time (min)	Tablet friability (%)	Tensile strength (MPa)
Run6MDZ	9	0.4	1.8
Run3MDZ	203	0.1	2.2

Since formulations did not include disintegrating agent, the fastest disintegration results suggested a disgregating effect of the absorbent guar gum which might be attributable to factors such as wettability, swelling capacity and viscosity. As already discussed, xanthan gum was the least wettable absorbent used, but guar gum and k-carrageenan did not show significantly different wetting behavior, thus, differences in their disintegration ability should respond to the other factors. Guar gum dissolves readily in water at room temperature, while a potassium salt of kappa carrageenan such as Gelcarin GP812 NF requires hot water for solubilization, but swells in cold water and produces strong gels [35,36]. Gel formation tends to counteract the disintegration promoted in first instance by polymer swelling, since high viscosity in the tablet surface would prevent water penetration into the matrix [37]. Two-way ANOVA confirmed that also binder type and the interaction between binder and absorbent type had significant effects on disintegration time ($p = 0.00$), though absorbent effect prevailed. The presence of povidone tended to decrease disintegration time. Another trend revealed the effects of both formulation factors on tensile strength. This tablet attribute was favored (high values in Dim3 in Figure 3b) by the presence of guar gum and copovidone, while the softest tablets were obtained from carrageenan granulates. This behavior could be explained by the low glass transition temperature (Tg) of the carrageenans. The carrageenans are at room temperature in the rubbery state [25], while xanthan and guar gums [38,39] are in the glassy state. A low Tg would tend to promote less deformation of polymer fibers, negatively impacting on mechanical interlocking [25]. Nevertheless, the three absorbents proposed in this study rendered tablets strong enough to counteract the negative effect of the rather high percentage of elastic recovery of this type of excipients.

The effect of binder type on the behavior of the formulations divided samples into three groups, which were confirmed by CA. The dendrogram, a graphical display of the result of CA, is shown in Figure 4.

According to CA, the three clusters were relatively distant from one another and were formed as follows:

First cluster: runs 1 and 2; granulates containing only PVP as binder. Thus, this cluster was formed by the granulates with the highest 50th percentile, span and compressibility index, and the lowest density, which also produced tablets with the lowest friability.

Second cluster: runs 4, 7 and 9; granulates containing a combination of both binders. Therefore, this cluster was formed by the granulates with intermediate response values between formulations containing either PVP or copovidone.

Third cluster: runs 3, 5, 6 and 8; formulations containing only copovidone plus the PVP granulate containing xanthan. Thus, this last cluster included the granulates characterized by the lowest compressibility index and rather low 50th percentile and span, while presenting medium to high density, which also produced tablets with medium to high friability and tensile strength.

The lower concentration-dependent increase in viscosity and the

smaller median particle size of PVP K15 with respect to copovidone [40,41] could throw light upon the performance of the granulation process. The granule-formation mechanism in the MADG process is the same as that in conventional wet granulation [7]. It is also known the effect of binder viscosity in growth rate of granules in the conventional wet granulation method, which is explained by particle deformability [42]. Therefore, less viscous PVP could be better distributed as a tacky binder throughout the powder bed, facilitating nucleation and granule growth, and leading to higher 50^{th} percentile. Conversely, the lower viscosity of this binder could also be responsible for the higher span values found, since a more deformable system could generate larger granules, but not necessarily facilitating a uniform particle size distribution.

In summary, results were indicative of a successful granulation process, even more considering that not directly compressible fillers and moisture absorbents exhibiting rather poor compactability were present over 80% w/w of total concentrations in all of the experimental runs. The second and third clusters grouped the formulations which showed the best behavior towards the production of tablets.

Metronidazole tablets: Runs 3 and 6 were selected to produce metronidazole tablets (see Table 4) to verify if different drug release profiles were achieved in presence of the same binder with moisture absorbents guar and xanthan gum, as the least and the most retarding agents, respectively.

Tablets with appropriate aspect and mechanical strength (see Table 5), presenting results of relative standard deviation of tablet weight below 1.5% were obtained. Drug release profiles are presented in Figure 5.

Guar gum-metronidazole tablets (Run6MDZ) did not require the addition of a disintegrating agent to achieve fast disintegration (less than 10 min) and were able to release more than 85% of the API in 30 minutes. Similar results reporting fast release of highly water-soluble APIs when guar gum was used as hydrogel in solid delivery systems were found in literature [16]. In contrast, tablets containing xanthan gum (Run3MDZ) showed long disintegration times and required near 6 hours to release 85% of metronidazole. These results supported the usefulness of hydrogel-forming polysaccharides as versatile moisture absorbents, also able to aid in modulating drug release in MADG.

The results here presented expose interesting perspectives towards a broader range of MADG moisture absorbents which could provide more versatility in MADG formulation. The prospect of combining the effect of moisture absorbents with that of binders in order to control drug release from delivery systems obtained by a convenient process such as MADG is undoubtedly auspicious.

Conclusions

In the present study, the three hydrogel-forming polysaccharides selected as moisture absorbents produced tablets with appropriate physical properties, and significantly different disintegration behaviors and drug release profiles. Therefore, guar gum, k-carrageenan and xanthan gum should be regarded as promising candidates for either immediate or extended release tablet formulations produced by MADG, an energy and time efficient granulation process. Knowledgeable choices made regarding moisture absorbent agents might make the absorption step of MADG more versatile and even minimize the total number of formulation components. Consequently, an advantageous process such as MADG would find its development, validation and scale up further facilitated and could become a more eligible process for producing modified release products. The impact of absorbent wettability properties on tablet disintegration time is relevant, however, requires taking into consideration also binder characteristics. The presence of copovidone, alone or in combination with a lower percentage of another binder such as povidone, proved to be a good choice for granulating a high load (80%) of not directly compressible materials by MADG.

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