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Hydrogel-Based Granular Phytostrengtheners for Prolonged Release: Production and Characterization

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Soil wellness is an indispensable requirement to obtain fruits and vegetables with finest quality and with high yields. To the purpose, periodical administrations of nutrients, as well as phytostrengtheners could be required. Crucial goals to maximize the economic and environmental sustainability of the whole cultivation are the decrease of the dosages number together with the increase of the active substance availability within the soil. With these aims a controlled release phytostrengtheners encapsulated in a granular Hydroxypropyl methylcellulose matrix has been developed exploiting the wet granulation process. The granular product has been analyzed in terms of Particle Size Distribution (PSD), morphology and flowability. The results showed the effectiveness of the granulation process and the good flowability of the granules, highly desirable features for the product handling and commercialization.

1. Introduction

The continuous population growth, along with the increased food quantity and quality requirements, binds the agricultural sector to use ever-larger quantities of fertilizer, phytostrengtheners and agrochemicals. However the massive use of these products presents economic and environmental drawbacks. The mainly environmental impacts can be linked to leaching phenomena that can cause ground water contamination or aquatic eutrophication as well as to soil pollution (Falciglia and Vagliasindi, 2013) and emission of greenhouse gases (e.g. nitrous oxides) (Chien et al., 2009). Hence, it is of vital importance to conceive and develop systems that can boost production and mitigate environmental impacts.
To the purpose, Controlled Release Systems (CRSs) can represent a valid tool to achieve these goals, releasing ideally nutrients/agrochemicals along with the plant needs, for an entire cultivation cycle (Blouin and Rindt, 1967, Shaviv, 2001, Sempeho et al., 2014). Looking at Controlled Release Fertilizers (CRFs), they can be classified according to several authors (Trenkel, 1997, Shaviv, 2005, LinShu et al., 2008) in three major categories: i) Organic compounds: that can be sub-classified in natural or synthetic and/or in chemical decomposing or biological decomposing compounds; ii) Water soluble fertilizers with physical barriers: it can be sub-divided in coated granules and fertilizer matrices; iii) Inorganic low solubility compounds.
The CRSs through coating technique have been the most studied, since the early 1960's when the Tennessee Valley Authority proposed the process for the production of sulfur coated urea granules (Blouin and Rindt, 1967). However, this system are subjected to the burst of the coating due to osmotic pressure and the complete release of the core content (Shaviv, 2005, LinShu et al., 2008). In attempt to overcome the "catastrophic release", synthetic polymers (e.g. polyolefin, polyacrylic acid and mostly polyurethane) have been used to coat granules.
On the other end the CRSs based on matrix encapsulation have been less investigated with respect to coated formulations (Shaviv, 2001), but particular emphasis, in the last years, has been pointed toward hydrophilic matrices able to form hydrogels (Rudzinski et al., 2002). Hydrogels are capable of imbibing large amounts of water or biological fluids (Peppas et al., 2000). When an Active Ingredient (AI) is encapsulated in this kind of system its release mechanism become quite complex and several steps can be identified. Briefly, when a dry

hydrogel matrix enters in contact with water, the solvent starts to penetrate inside the system, polymeric chains unfold so that a glass-rubbery transition occurs and a gel-like layer is formed. In the swollen region the contained AI molecules can easily diffuse toward the outer dissolution medium, once that they are dissolved. These properties have brought hydrogels to be one of the most abundant CRSs in the pharmaceutical field and their extension to the agricultural applications is particular attractive due to their additional property of water retention, that reduce water consumption and irrigation frequency, especially in drought areas (Azeem et al., 2014). Several attempts to produce hydrogel-based CRS for agricultural sector have been made, for both pesticides and fertilizers, using alginate (Roy et al., 2009), ethyl cellulose (Cea et al., 2010), chitosan (Corradini et al., 2010, Jamnongkan and Kaewpirom, 2010) and others natural and semi-natural polymers mostly in the forms of nano and micro-particles (Sempeho et al., 2014, Roy et al., 2014, Rudzinski et al., 2002). However when it comes to hydrogel-based system, hydroxypropyl methylcellulose (HPMC) is one of the first choices for matrix formulation due to its nonionic nature, which makes its swelling behavior independent from the environmental pH, and cost effectiveness. It has been extensively used in pharmaceutical applications (Cascone et al., 2014) and very recently it has been employed with promising results in CRFs (Ureña-Amate et al., 2011, Melaj and Daraio, 2014).

1.1 Aim of the work

The aim of this work is to investigate the feasibility of Hydroxypropyl methylcellulose (HPMC) as controlled release granules for agricultural applications. Further aim is the characterization of the produced granules in terms of morphology, flowability, and granulometric properties.

2. Materials and methods

2.1 Materials

Powders of HydroxyPropyl MethylCellulose (HPMC, Methocel K4M) were kindly supplied by Colorcon, Varese, Italy. Tequil® Multi, the reference phytostrengthener, was provided by Fertenia Srl, Bellizzi, Italy.

2.2 Granulation process

The wet granulation process was performed with a Caleva Multi Lab (from Caleva Process Solutions). Each granulation batch was carried out with 5 g of HPMC powder and 4 mL of wetting phase. Two different granular products were produced, varying the wetting phase composition: for the first one, “GC”, 4 mL of pure Tequil® Multi were used, for the second one, “GD”, 4 mL of Tequil® Multi diluted 1:5 with distilled water were used. The operative conditions were: blades rotation of 60 rpm and granulation time of 300 s with the addition of the wetting phase drop by drop with a syringe during the first 120 s. The product obtained from the granulator was forced to pass through a sieve with a mesh opening of 2 mm to emulate a milling process and therefore limiting the particle size distributions (PSDs). The granules were dried out in oven at 80°C overnight.

2.3 Particle Size Distribution (PSD) from image analysis

The PSD of the granular products were obtained through image analysis. Several samples pictures were taken and analyzed with the software Image-Pro Plus 6.0 (from Media Cybernetics) obtaining the mean diameter of each granule. The advantages of the PSD determination through image analysis, apart from gathering information on the particles shape, lie mainly in the possibility to choose the size intervals in which the particles have to be counted (e.g. not being constrained to a certain number of sieves). In this work a $\sqrt{2}$ progression of the intervals dimension limits was applied obtaining 18 interval classes (Allen, 2003): from 0 to 3,620.39 µm. The cumulative undersize numeric discrete distribution can be easily obtained considering its definition:

$$Q_{0,j} = \sum_{i=1}^{j} \frac{n_i}{n_{tot}} \quad (1)$$

Where with the subscript “0” the numeric distribution is indicated (related to the power of zero of the particles dimension), j characterizes the j^{th} class, n_i denotes the number of particles in the i^{th} class and n_{tot} the total number of particles. Equation (1) furthermore highlight the meaning of “undersize” since its value expresses the numeric fraction of particles below the upper limit size of the j^{th} class. Furthermore it can be preferred to express the PSD in terms of cumulative undersize mass discrete distribution, weighing the importance of the particles dimensions not to their number but to their mass, that can be more significant in the processes of powder handling.

$$Q_{3,j} = \sum_{i=1}^{j} \frac{m_i}{m_{tot}} \quad (2)$$

Where with the subscript "3" the mass distribution is indicated (related to the power of three of the particles dimension). In this case m_i represents the mass of particles in the i^{th} class and m_{tot} the total mass of particles.
The image analysis allows to obtain directly, from the raw data, only the numeric distribution since the analysis is based on the quantification of the number of particles and not of their mass/volume. However with some considerations it is possible to derive the mass distribution as well (Caccavo, 2011).

2.4 Flowability

The product flowability was analyzed through the determination of the Carr's Index (CI) and Hausner Ratio (HR) (McGlinchey, 2008) and the angle of repose. The CI and HR are functions of the bulk density (ρ_B) and tapped density (ρ_T). The bulk density of a powder is the ratio of the mass of an untapped powder sample to its volume, including the contribution of the interparticulate void volume. The tapped density, instead, is an increased bulk density attained after mechanically tapping a receptacle containing the powder sample (Pharmacopoeia, 2014). In this work the bulk density was determined gently pouring 2 g of the sample in a graduated cylinder: the ratio between the mass and the volume occupied gave the bulk density. The tapped density was determined after a tapping procedure achieved with 100 manual taps, the ratio between the sample mass and the tapped volume gave the tapped density. From ρ_B and ρ_T the HR and CI can be easily calculated according to their definitions:

$$\begin{cases} HR = \frac{\rho_T}{\rho_B} \\ CI = \left(1 - \frac{\rho_B}{\rho_T}\right) \cdot 100 \end{cases} \quad (3)$$

2.5 Scanning Electron Microscopy (SEM) morphology

The granules morphology were analyzed with the scanning electron microscope Zeiss DSM 962 (Zeiss, Germany). Samples were fixed over an adhesive carbon tab, previously stuck to an aluminum stub and coated with gold (layer thickness 250 Å) using a sputter coater (B7341, Agar Scientific, Stansted, UK). All the images were taken with a zoom of 300x.

2.6 Tequil® Multi characterization

The Tequil® Multi was characterized in terms of dry weight content, using the moisture analyzer MB45 (Ohaus Europe, Switzerland). The product showed an amount of dry weight content of 0.6145 g_{Teq}/mL_{sol} that can be intended as the concentration of AI in the commercial product.
The product was characterized spectrometrically using a LAMBDA 35 UV/Vis Systems spectrophotometer (PerkinElmer, USA). The samples were analyzed using a previously developed technique (Cascone et al., 2012) at λ=280 nm.

3. Results and discussion

3.1 Particle size distributions

The PSDs, in terms of cumulative undersize mass distributions (Q_3), of GC and GD and a granules picture are shown in Figure 1. As it can be seen GC and GD reveal very similar PSDs where the 70% of the granules have a mean diameter greater than 0.7 mm. To characterize the PSDs with an average value the median diameter (d_{50}) can be used, that is the diameter for which one half of the total mass of particles are larger, and one half smaller.

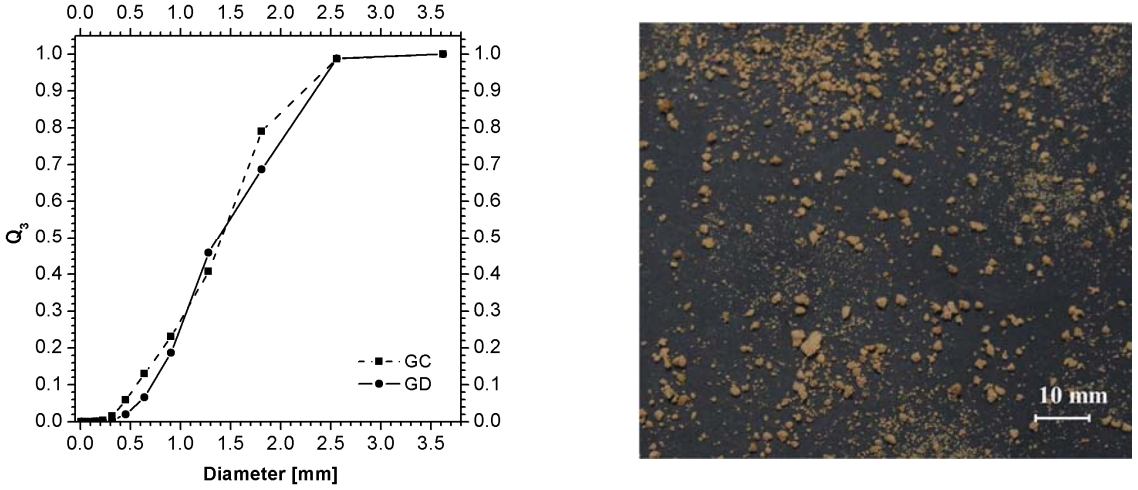

Figure 1. Particle size distributions in terms of cumulative undersize mass distributions (left) and granules picture (right).

Therefore, in Figure 1, it is the diameter for which Q_3= 0.5 that correspond to 1.4 mm for both the granulated products. From the graph it can even be seen that approximately the 20% of the particles have a mean diameter greater than 2 mm, that correspond to the mesh opening of the sieve used for the milling step. This result can be explained considering that the wet granules forced to pass through the sieve acquire an elongated shape, leading their mean diameter to be greater than 2 mm. An ultimately consideration, looking at Figure 1, can be made on the effectiveness of the wet granulation process carried out in this work in terms of particles size enlargement. Indeed the final granules dimensions were far above the initial HPMC powders dimensions, defined "fine particles" (10-150 μm), from the producer (Dow, 2000).

3.2 Granules loading

The amount of Tequil® Multi encapsulated in the granules were theoretically calculated and experimentally quantified. The theoretical amount can be evaluated starting from the quantity of HPMC and Tequil® Multi (in mass) employed in the granulation process obtaining the 9% wt/wt and the 33% wt/wt of Tequil® Multi in the granules, respectively for GD and GC. The experimental quantification was done dissolving a known amount of product in a certain volume of distilled water. The resultant solutions were analyzed spectrometrically and the amount of Tequil® Multi quantified. The results gave the 9% wt/wt and the 32% wt/wt for GD and GC respectively, validating the quantitative method to analyze the Tequil® Multi described in the paragraph 2.6.

3.3 Flowability and morphology

In Table 1 the bulk and tapped densities, HR, CI are reported. To emphasize the granulates results are reported in the same table the value obtained with the HPMC powder as well. Looking at the granulate bulk and tapped densities it can be seen as GD presents values greater than GC. Considering that both the systems have similar PSDs, therefore the same degree of void, the higher bulk and tapped density values can be explained only if GD presents higher particle density, therefore more compact granules. The Hausner Ratio and Carr's index depict GD and GC both as "excellent flow granules" whereas the initial HPMC powders have very poor flow properties and tend to be cohesive.

Table 1. Products flowability and flow description.

	ρ_B $[kg/m^3]$	ρ_T $[kg/m^3]$	HR [–]	CI [–]	Flow Description (Nedderman, 2005)
HPMC Powder	333.0 ± 0.0	468.6 ± 6.4	1.41	28.9	Cohesive powders – poor flow
GC	285.7 ± 0.0	317.5 ± 5.0	1.11	10.02	Free flowing – excellent flow granules
GD	400.0 ± 0.0	438.0 ± 5.6	1.10	8.68	Free flowing – excellent flow granules

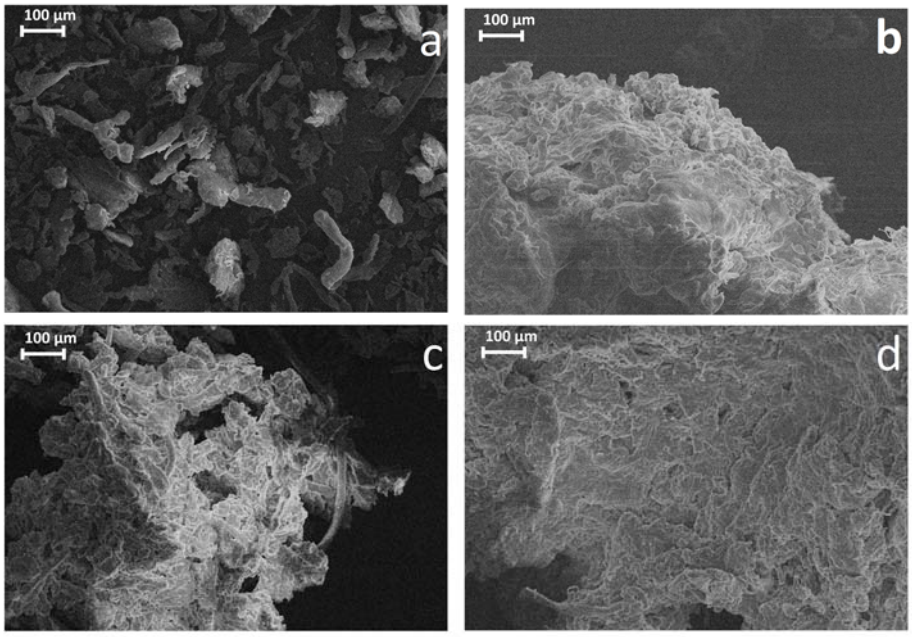

Figure 2. SEM pictures at 300x of HPMC powder (a), HPCM granulated with distilled water (b), GC (c) and GD (d).

In Figure 2 are reported the SEM images of HPMC powders (a), HPMC granules obtaining with a wetting phase of pure distilled water (b), GC (c) and GD (d). As it can be seen, the morphology of GD can be collocated in between the one of HPMC granules and GC. Indeed in the first (Figure 2\b) the single particles of HPMC powders (Figure 2\a) are no more recognizable due to a great cohesion between them. On the opposite, in GC (Figure 2\c) the single HPMC powders particles are in such a way still identifiable, creating a less compact structure with higher internal porosity. Between these two extreme morphologies the one of GD (Figure 2\d) can be placed, where are present zones in which the single powders particles are distinguishable and zone in which they are not. These granules morphologies well explain the density and mechanical results, confirming the more compacted structure of GD with respect to GC. The reason of such a different morphology can be explained considering the different composition of the wetting phase employed. The distilled water seems to have better binding properties with respect to Tequil® Multi and this behavior is emphasized in the comparison between HPCM granules and GC where pure water and pure Tequil® Multi were used, respectively.

4. Conclusions

In this work an hydrogel-based granular system for controlled release in agriculture has been produced and characterized. A commercial liquid phytostrengthener has been encapsulated via wet granulation process in HPMC matrices, obtaining a granular product. Two different compositions of the wetting phase have been used, one with the pure liquid phytostrengthener and another with a water solution of the phytostrengthener, obtaining two different products, namely GC and GD, respectively. These granules have been analyzed in terms of particle size distribution using the image analysis method and the results have shown similar distribution between them. The granulated products have been investigated in terms of flowability characteristics measuring the bulk and tapped densities. The results highlighted the good products flowability, highly desirable for the powder handling processes, and underlined a greater GD granules density respect to GC. The GD has shown a more compact structure, with less void and better HPMC powders coalescence, with respect to GC. The reason of such a different morphology, that in turns is responsible for the differences in density, has been attributed to the different composition of the wetting phase.

In conclusion the controlled release systems developed in this work have shown good flowability characteristics, indispensable requirements for the production and commercialization. Further studies will be devoted to characterize the release pattern of these HPMC-based granular phytostrengtheners.

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