Novel Hydrophilic Matrix System with Non-Uniform Drug Distribution for Zero-Order Release Kinetics

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ABSTRACT

A decrease in the release rate over time is typically encountered when dealing with hydrophilic matrix systems for oral prolonged release due to progressive increase of the distance the drug molecules have to cover to diffuse outwards and reduction of the area of the glassy matrix at the swelling front. In order to solve this issue, a novel formulation approach based on non-uniform distribution of the active ingredient throughout the swellable polymer matrix was proposed and evaluated. Various physical mixtures of polymer (high-viscosity hypromellose) and drug tracer (acetaminophen), having decreasing concentrations of the latter, were applied by powder-layering onto inert core seeds. The resulting gradient matrices showed to possess satisfactory physico-technological characteristics, with spherical shape and consistent thickness of the layers sequentially applied. The non-uniform matrix composition pursued was confirmed by Raman mapping analysis. As compared with a system having uniform distribution of the drug tracer, the multi-layer formulations were proved to enhance linearity of release. The simple design concept, advantageous technique, which involves no solvents nor high-impact drying operations, and the polymeric material of established use make the delivery platform hereby proposed a valuable strategy to improve the performance of hydrophilic matrix systems.

INTRODUCTION

Tableted matrix systems for oral prolonged release of common cylindrical shape typically display a decrease in the rate of release over time due to progressive increase in the diffusional path the drug has to cover to reach the outer medium and concomitant reduction of the area at the solvent penetration front. Particularly in the case of hydrophilic matrices, an initial burst release may also be observed due to the fraction of drug present on the surface, which is released when the outer polymer particles are not fully swollen yet [1]. Because zero-order kinetics has long been sought to attain constant drug absorption rate for a predetermined period of time, thus providing the patient with constant drug levels between two successive doses, several attempts to address these issues have been reported in the literature. The resulting systems are intended to reach the goal of a linear release pattern by the use of different strategies, which may involve mechanical restriction of swelling, application of partial coatings and/or design of modified geometries [2–10]. Overall, these approaches would be aimed at restraining the gradual extension of the diffusion path or progressively broadening the area at the solvent penetration front within the matrix.

In addition, gradient systems, wherein the drug concentration increases from the outside towards the inside, have been described [11–18]. Such systems may be obtained by controlled extraction processes, coating/layering techniques or, alternatively, emerging fabrication methods, such as 3D printing and

electrostatic deposition, that are still poorly exploited in the pharmaceutical field [19–23]. Coating is mainly based on liquid vehicles that not only require time- and energy-consuming drying phases, but also may bring about stability issues. In this respect, aqueous spray-coating would especially be critical when using hydrophilic polymers tending to generate too high viscosities and involving the use of diluted solutions [24,25]. Notably, powder-layering, wherein coating materials are directly layered as solids onto inert starting cores, may overcome most technical issues connected with liquid-based processes [26,27]. For these reasons, it was deemed to be an alternative technique that could advantageously be exploited for manufacturing of hydrophilic gradient matrices.

Accordingly, the aim of the present study was to *i)* design a hydrophilic matrix system with non-uniform drug distribution (Non-Uniform Drug Distribution Matrix, NUDDMat) for prolonged release, intended to ultimately provide zero-order kinetics, *ii)* study the feasibility of powder-layering in the relevant manufacturing through application of successive layers having decreasing drug concentrations, and *iii)* evaluate the *in vitro* performance of the resulting prototypes.

MATERIALS AND METHODS

MATERIALS

Acetaminophen fine powder British Pharmacopoeia (AAP, CFM, Italy) (water solubility 14.8 mg/mL, true density 1.13 g/mL [28–30]) was used as the tracer and high viscosity hypromellose (HPMC, Methocel® K15M, Colorcon, Italy) (apparent viscosity, 2% in water at 20 °C 6138–9030 mPa*s, USP substitution type 2208, true density 1.32 g/mL [31–33]) was selected as the hydrophilic swellable polymer. Lactose (Carlo Erba, Italy, true density 1.50 g/mL [34]) and dibasic calcium phosphate dihydrate (DCP, Emcompress®, JRS, Germany, true density 2.21 g/mL [35]) were evaluated as soluble and insoluble diluents. Fumed silica (Aerosil® 200, Evonik, Germany) was added as a glidant to the powder mixtures, and povidone (PVP, Kollidon® 30, BASF, Germany, true density 1.11 g/mL [36]) was used as the binder in aqueous solution.

Nonpareil microcrystalline cellulose (MCC) pellets having nominal diameter of 850 µm were chosen as the starting cores (Cellets® 700, Pharmatrans-Sanaq, Switzerland, true density 1.46 g/L [37]).

METHODS

Manufacturing of tableted and layered units

According to formulas set up during the experimental work, reported in the Results and Discussion section, powder blends to be tableted or layered were obtained by mixing in Turbula® (Willy A. Bachofen, Switzerland) at 24 rpm for 20 min.

Tableting was performed by a rotary tablet press (mod. AM8S, Officine Meccaniche Ronchi, Italy) equipped with 4 mm diameter concave punches (4 mm curvature radius) at 7 kN compression force (batch size 50 g). The nominal weight of matrices was 45 mg.

98   Powder layering was performed by a fluid bed (GPGC 1.1, Glatt, Germany) equipped with rotor insert. The

99   operating conditions set up were as follows: nozzle port size 1.2 mm, air temperature in 30 °C, product

100   temperature 26-28 °C, air temperature out 23 °C, air flow 70 m^3/h, nebulization air pressure 2 bar, product

101   pressure 1100 Pa, disk rotation speed 700 rpm, liquid binder feeding rate 12 g/min, powder feeder rate 20

102   g/min. For any layering step, 500 g of starting substrate was loaded into the processing chamber. Powder

103   addition was accomplished via forced powder feeder while spraying a binding solution onto preheated

104   substrate cores. The diameter and weight of the coated units were regularly checked in-process by withdrawing

105   samples (n=100) at prefixed time intervals. After each layering step, a post-processing drying phase was

106   performed at inlet air temperature of 60 °C for 30 min. Process yield was calculated as the percentage weight

107   ratio between the layered units and the employed materials (seeds, layering powders, binder).

108

109   *Physico-technological characterization of tableted and layered units*

110   Tableted (n=20) and layered (n=100) units were checked for weight and for thickness and/or diameter by a

111   precision calliper (CD 150, Mitutoyo, Italy).

112   The aspect ratio was calculated dividing the maximum by the minimum diameter of each unit, as measured by

113   digital microscope (Dino Lite Pro AM 413T, Italeco, Italy) (n=20).

114   Friability was assessed according to Eur. Ph. 9.2 by a friabilometer (mod. EF-2, Electrolab, Italy) rotating at

115   25 rpm for 4 min. 6.5 g of units was used for the measurements. The data obtained were expressed as loss-on-

116   weight percentages.

117   Crushing strenght (n=10) was measured by the equipment reported in Eur. Ph. 9.2 (mod. T3, Erweka,

118   Germany).

119   Porosity (*E*) of units, expressed as percentage, was calculated according to the equation:

120

121    $$E\ (\%) = \left[1 - \frac{V_t}{V_b}\right] \cdot 100 \qquad (1)$$

122

123   where Vt is the true volume and Vb is the mean bulk volume.

124   Cross-section morphology was analyzed by a scanning electron microscope (SEM; Sigma, Carl Zeiss,

125   Germany). Samples were gold-sputtered using a plasma evaporator under vacuum, and photomicrographs were

126   acquired at an accelerated voltage of 10 kV at differing magnifications.

127

128

129   *Release testing of tableted and layered units and data analysis*

130   Samples corresponding to an overall amount of 50 mg of AAP were tested for release by a Eur. Ph. 9.2

131   dissolution apparatus (mod. 2100B, Distek Italia, Italy) equipped with rotating baskets using 900 mL of

132   purified water at 37 ± 0.5 °C stirred at 100 rpm (n=3). AAP was assayed by spectrophotometer at 243 nm

133   (Lambda 25, Perkin Elmer Italia, Italy) after verifying agreement of results with a HPLC method according to

USP 40-NF 35 [38]. Samples of medium were collected at 4 selected time points (0.5–70.0 μg/mL concentration range) during the release test. Each sample was analyzed ($n = 6$) by both HPLC (column: C_{18} at 40 °C, mobile phase: deionized water for HPLC/acetonitrile/perchloric acid 3000:1000:3, V/V/V, at pH 2.4, flow rate: 1.2 mL/min, detection: UV at 248 nm, injection volume: 40 μL) and UV using freshly prepared standard solutions as a reference. The 95% confidence intervals for the differences in the measured concentration means (UV minus HPLC) fell in the ±2% range with respect to the HPLC mean, in compliance with typical acceptance criteria [39]. For statistical comparison of release profiles, similarity factor f_2 was applied. $f_2 \geq 50$ (50-100) indicated similarity [40].

Release data from UDDMat systems were analyzed according to the equation:

$$\frac{M_t}{M_\infty} = kt^n \qquad (2)$$

where M_t/M_∞ is the drug fraction released at time t, n exponent indicates the mechanism/kinetics of release and k is a constant incorporating structural and geometrical characteristics of the matrix. Analysis of data was performed in the portion of the curve where M_t/M_∞ <0.60, and confidence intervals (c.i.) at 95% were calculated [41–43].

Equation (2) was also used to fit release data from NUDDMat systems. In this case, the portion of the curve wherein M_t/M_∞<0.90 was analyzed, and n values were used for descriptive purposes only to highlight progressive shift toward linearity. When n was = 1, the units were considered, from a merely phenomenological point of view, to behave as a zero-order release system, and values < 0.5 and >1 could also be taken into account.

The extent of linearity of release profiles was evaluated through the Durbin-Watson statistics, which enables to identify zero-order portions in each curve [42,44,45]. The release data were analyzed at time intervals of 1 h, between 0.05 and 0.90 fractions released (90% c.i.).

Raman mapping analysis

Raman mapping analysis was performed on cross-sectioned units using a confocal microscope XploRA Plus™ (HORIBA Italia, Italy), under the following conditions: acquisition time 0.6 s, laser 785 nm, grating 600 grooves/mm, objective 100x, spatial step size 40 μm, measured area 100×100 points (pixels) covering an area of 4000×4000 μm [46]. After acquiring Raman spectra of AAP, HPMC and DCP, the relevant identification was accomplished by a correlation algorithm through KnowItAll™ spectral database (HORIBA Italia, Italy). Hyperspectral mapping of the cross-sectioned systems was carried out moving the laser across the surface and acquiring a spectrum for each point. False color maps were generated after calibration of peaks related to the 3 components considered: green was assigned to AAP, blue to HPMC (or cellulose) and red to DCP. Maps were created by applying fast mapping mode on SWIFT™ accessory to reduce acquisition time while maintaining high resolution of spectra. The intensity ratio between the colors assigned to AAP and HPMC (AAP/HPMC ratio) was calculated. The AAP/HPMC ratio was associated to a false color (turquoise), and 2D

170 as well as 3D intensity maps were generated. Profiles of AAP/HPMC ratio versus diameter of the units were

171 also constructed.

172

173 **RESULTS AND DISCUSSION**

174

175 *Uniform Drug Distribution Matrix Systems*

176 With the aim of overcoming typical issues involved by hydrophilic matrices, namely the initial burst release

177 and gradual decrease in the release rate, an alternative strategy was explored for the relevant formulation and

178 manufacturing. Various swellable polymers have been proposed in the literature as matrix-forming agents,

179 such as hypromellose (HPMC), hydroxypropylcellulose (HPC) and polyethylene oxide (PEO) [1]. HPMC is

180 especially popular for the long-established regulatory acceptability and availability of different grades (degree

181 of substitution, molecular weight, particle size). Methocel® K15M, a high viscosity HPMC, was selected for

182 this study, and AAP was employed as an analytical tracer. Using a polymer percentage that could be considered

183 sufficient for formation of a non-disintegrating swellable hydrophilic matrix, systems based on a 30:70

184 HPMC/AAP mixture were first investigated (Table 1). Such systems were manufactured by either

185 conventional tableting (UDDMat T30) or powder layering (UDDMat P30) in order to assess the application

186 potential of the latter technique. For a successful outcome, powder layering requires the use of powders having

187 adequate flowing and adhesion properties. While the flowability of this blend proved to be suitable not only

188 for tableting but also for powder layering, the particle adhesion needed to be promoted by spraying a binder

189 solution for effective deposition. PVP, HPC and HPMC have been reported to be the most commonly used

190 binding agents for powder layering [47,48]. In particular, a 5% PVP (Kollidon® 30) solution was used, which

191 displayed satisfactory binding properties and suitable viscosity for nebulization.

192

194 *Table 1: tracer/polymer/diluent percentage composition of the different powder blends to be tableted or layered°*

System code	Layer	AAP (%)	HPMC (%)	Lactose (%)	DCP (%)
UDDMat (Uniform Drug Distribution Matrices) **T30**	-	70	30	-	-
P30	-	70	30	-	-
G20-80 1st		80	20	-	-
2nd		65	35	-	-
3rd		50	50	-	-
4th		35	65	-	-
5th		20	80	-	-
G20-100 #	5th	-	100	-	-
G20-100/2 #*	5th	-	100		
NUDDMat (Non-uniform Drug Distribution Matrices) **G30-30L** 1st		65	30	5	-
2nd		50	30	20	-
3rd		35	30	35	-
4th		20	30	50	-
5th		-	30	70	-
G30-30D 1st		65	30		5
2nd		50	30		20
3rd		35	30		35
4th		20	30		50
5th		-	30		70

205 *° 0.75% of fumed silica was added to each powder formulation*

206 *# composition of 1st-4th layers is the same as in NUDDMat G20-80*

207 ** nominal thickness 157 um*

208

209 The powder layering process was performed by rotary fluid bed starting from 850 µm MCC seeds. Preliminary
210 trials allowed the operating parameters to be adjusted. An efficient process was finally set up and a yield of
211 88.7% was reached. Powder layering was continued until the diameter of the units was approximately of 4 mm
212 as in the reference tableted matrices. The volume occupied by the starting seed was considered negligible.
213 Systems having an average weight of 45.75 mg $\pm$ 0.74 s.d. and friability of 0.3% were obtained, which turned
214 out comparable with tablets (weight 47.11 mg $\pm$ 0.29 s.d., friability 0.2%). Crushing strenght of layered
215 UDDMat units was significantly higher than that of tablets, i.e. 55 N $\pm$ 8 s.d. versus 24 N $\pm$ 5 s.d. ($p<0.01$),
216 respectively, probably owing to the use of an aqueous binder solution for layering. Interestingly, the two
217 different techniques led to very similar porosity for tablets and layered units: 4.8% and 4.9%, respectively.
218 Porosity, however, is known to only poorly influence the performance of hydrophilic matrices [49].

219

220

221 The basket dissolution apparatus was employed for release tests since the layered systems exhibited a certain
222 tendency to buoyancy. The use of sinkers with paddles was discarded because of major drawbacks in terms of
223 swelling constraints. The systems having uniform drug distribution, irrespective of whether they had been
224 manufactured by tableting or powder layering, showed a progressive decrease in the release rate over time
225 after a slight burst release phase (Figure 1). Indeed, when using equation (2), n of 0.832 (0.061 c.i.) and 0.775
226 (0.056 c.i.) obtained from tableted and layered matrices, respectively, highlighted non-fickian anomalous
227 release behaviour. The difference observed in n values between almost cylindrical compressed and spherical
228 layered matrices could be ascribed to the diverse shape, being included in the range predicted for cylinders
229 and spheres [50]. An almost superimposable release pattern was seen ($f_2 = 68.75$), indicating that neither the
230 use of powder layering for this particular application, nor the composition change required, i.e. the addition of
231 PVP in the binding solution, would significantly affect the release performance.

232
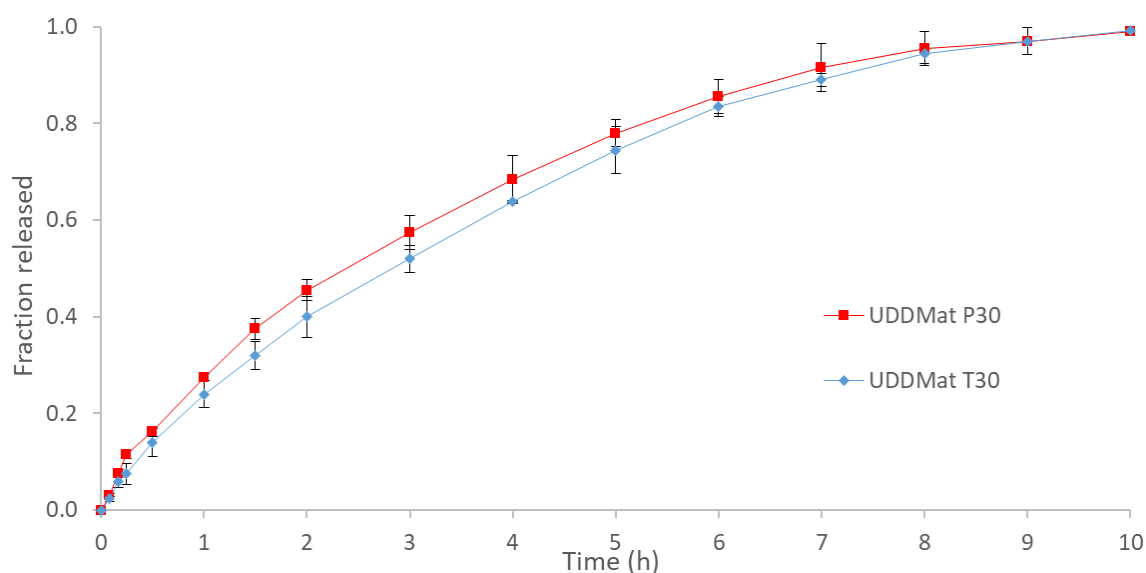
233

234 *Figure 1: release profiles from tableted (UDDMat T30) and layered (UDDMat P30) matrices with uniform drug*
235 *distribution. Vertical bars represent standard deviations.*

236

237 *Non-Uniform Drug Distribution Matrix Systems*
238 Powder layering was thus undertaken for the manufacturing of the Non-Uniform Drug Distribution Matrix
239 (NUDDMat). This system was designed to include 5 overlaid layers differing in drug concentration, which
240 decreased between contiguous layers from the inside towards the outside of the matrix according to a
241 descending staircase function, ultimately tending to an apparent overall linear mode [13,17]. In Figure 2, a
242 general outline of the NUDDMat system and layer-by-layer representation of the relevant theoretical drug
243 concentration profile are presented. The nominal thickness of each layer was 315 µm aiming at a final diameter

244 of 4 mm, as in the previous systems having uniform drug distribution, including the diameter of the core (mean
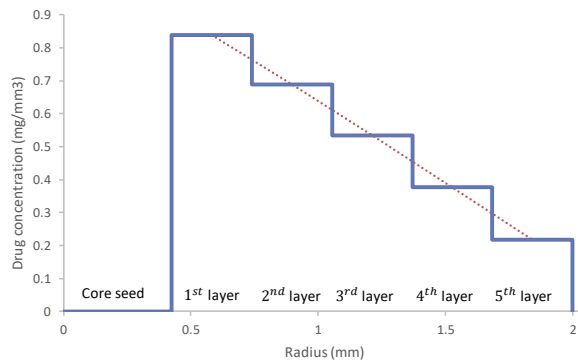245 diameter 850 µm).

246

247 a)
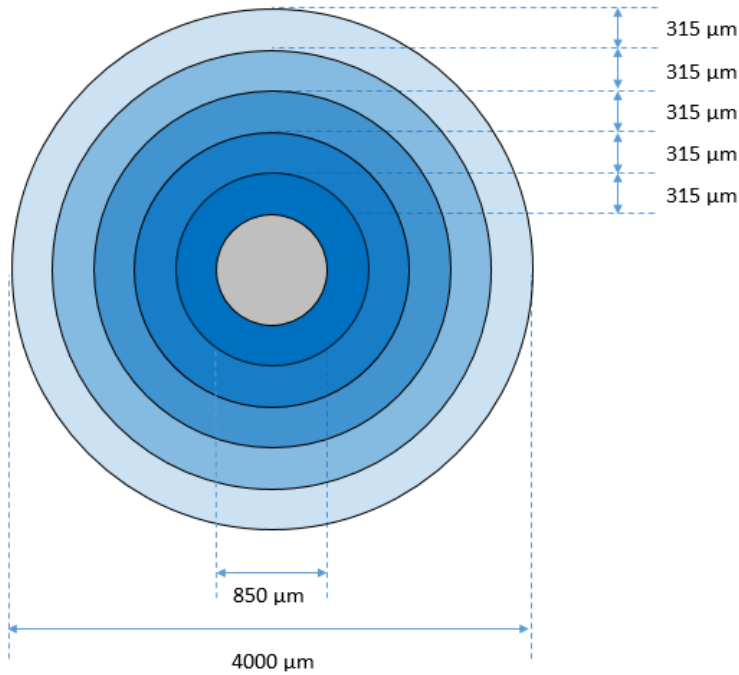
248

249 b)

254

255 *Figure 2: a) NUDDMat design concept (drug tracer concentration is indicated by color intensity); b) theoretical*
256 *tracer concentration pattern along the radius (the dotted line indicates the overall decreasing trend of*
257 *concentration).*

258 G20-80 was the first NUDDMat system prepared, according to the above-illustrated design concept. The
259 nominal percentage composition of each layer was set based on prefixed AAP/HPMC ratios reported in Table
260 1, taking the need for binder and glidant into account. PVP and fumed silica were maintained at 3.00% and at
261 0.72%, respectively.

In particular, the percentage of PVP was calculated based on a 5:3 weight ratio between layered powder and 5% w/w binding solution. The amount of materials required for each layer was calculated based on the true density of the formulation components by assuming a layer porosity of 5% (Table 2).

Table 2: nominal diameter, volume, weight, drug content and drug concentration, cumulative and for each layer, in NUDDMat G20-80 system

| Unit	Cumulative diameter (mm)	Layer volume (mm³)	Cumulative volume (mm³)	Layer weight (mg)	Cumulative weight (mg)	Layer drug content (mg)	Cumulative drug content (mg)	Layer drug concentration (mg/mm³)
Core seed	0.85	-	0.32	-	0.50	-	-	-
1-layer	1.48	1.38	1.70	1.50	2.00	1.16	1.16	0.84
2-layer	2.11	3.22	4.92	3.55	5.55	2.22	3.38	0.69
3-layer	2.74	5.85	10.77	6.50	12.05	3.13	6.51	0.53
4-layer	3.37	9.26	20.03	10.39	22.43	3.50	10.01	0.38
5-layer	4.00	13.46	33.49	15.22	37.66	2.93	12.94	0.22

It ensues that the theoretical total amount of drug tracer for each unit was approximately 13 mg, corresponding to 34.4% of the overall mass, the weight percentage of the starting seed being about 1.3%.

Due to their differing compositions, the powder mixtures employed for the manufacturing of NUDDMat G20-80 exhibited diverse flow properties ranging from very poor to poor according to Eur. Ph. 9.2 classification (compressibility index from 32% of the inner layer formulation to 28% of the outer one). Nevertheless, the powder feeding device in use allowed all mixtures to be loaded into the processing chamber of the fluid bed at a sufficiently reproducible rate consistent with continuous mode of dosing, and no formulation changes were needed. Powder adhesion onto the cores was expectedly enhanced with increasing percentage amounts of polymer in the mixtures. However, a 5% PVP solution, which was sprayed when layering the 30:70 HPMC:AAP mixture within the preparation of UDDMat P30, proved also effective with the most critical 20:80 blend, i.e. the formulation of the innermost layer. On the other hand, although simple spraying of water would have been possible with the mixtures having higher HPMC content, the same type and amount of binder solution was utilized for consistency in all powder layering steps. During the whole process, a 5:3 weight ratio was maintained between powder dosing rate (20 g/min) and binder spraying rate (12 g/min), so that the percentage of PVP could be the same in all layers.

The powder layering process was run in 5 successive steps, each corresponding to a single layer, starting from a 500 g load of either inert seeds or intermediate layered units. By assuming a yield of 90%, the amount of powder formulation to be applied for each layer was calculated so that the desired 315 µm increase in thickness

could be reached. When the whole quantity of powder blend needed per layer was loaded, the resulting layered units underwent a drying phase and were then checked for weight, diameter, porosity, crushing strenght, friability and aspect ratio (Table 3). The increases in weight and diameter were close to the expected values, although slightly higher data were generally obtained because of the process yield being greater then assumed. Porosity values turned out slighly higher than predicted with respect to those exhibited by UDDMat systems. The overall mechanical characteristics were proved satisfactory. Indeed, friability was approximately 0.4%, and crushing strenght was remarkably higher than in the case of both tableted and layered UDDMat systems having 30% of HPMC. The aspect ratio was around 1 thus indicating that NUDDMat G20-80 system had spherical shape, as confirmed by visual inspection (Figure 3).
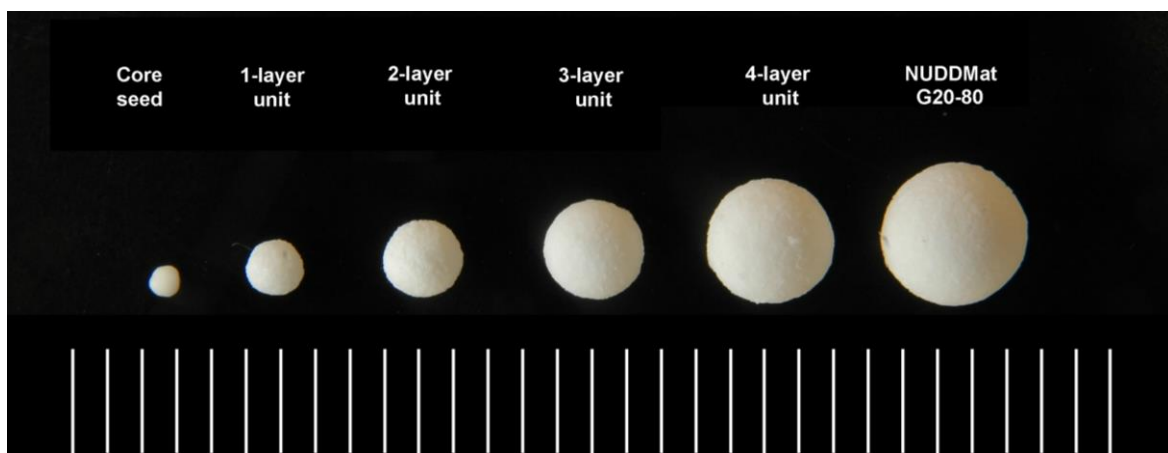
Figure 3: units ranging from the core seed to the final NUDDMat G20-80 system (scale in millimeters).

The expected internal onion-like structure of NUDDMat G20-80, generated by discontinuous processing through application of powders with differing compositions, can barely be distinguished from SEM photomicrographs of a cross-sectioned unit (Figure 4). The dimple that is visible in the center of the system was left by the core seed, which was removed upon sectioning.
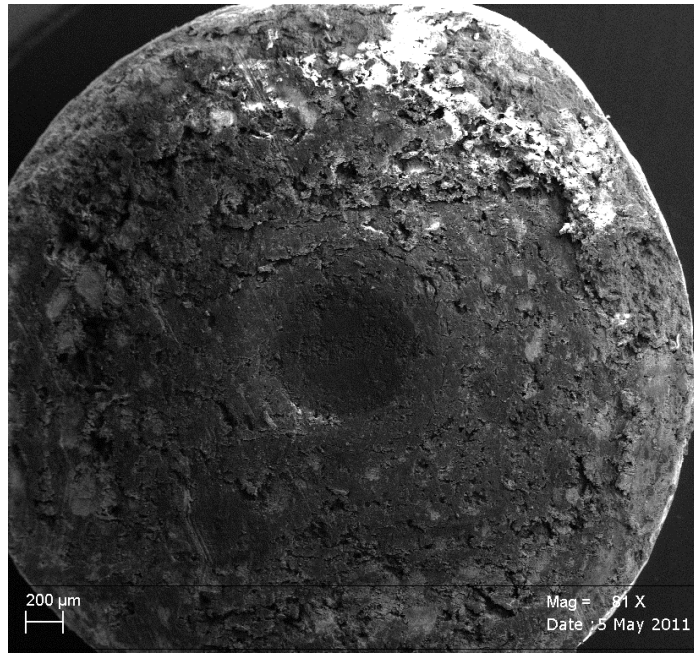
Figure 4: SEM photomicrograph of a cross-sectioned NUDDMat G20-80 unit.

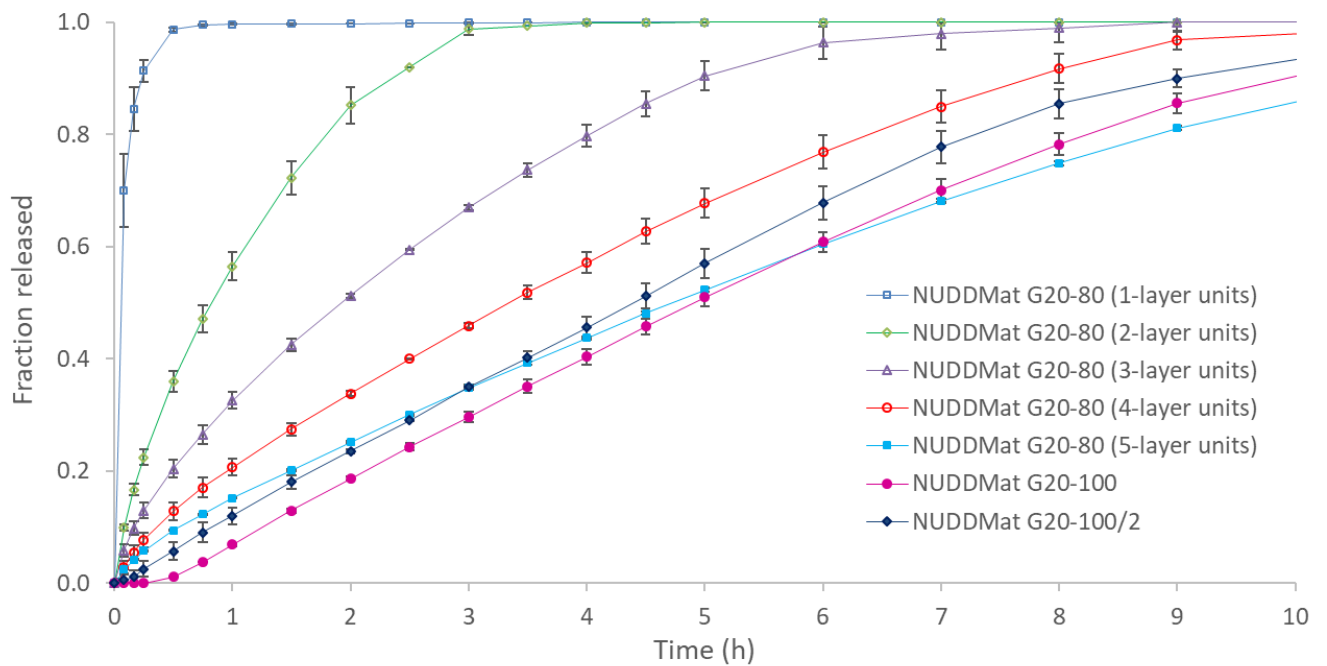The release profiles of the final NUDDMat G20-80 system and of the relevant intermediate units having 1 to 4 layers are reported in Figure 5.

Figure 5: release profiles from systems NUDDMat G20-80 and relevant intermediate units, NUDDMat G20-100 and NUDDMat G20-100/2.

315   The n values resulting from data processing by exponential equation (2), here used for merely descriptive

316   purposes, progressively increased thus pointing out a shift of the curves towards linearity (Table 4).

317   One-layer units released the drug tracer rapidly due to a limited percentage amount of polymer. Indeed, the

318   matrix structure could not withstand rapid erosion/disintegration, and the n value provided no meaningful

319   information. On the other hand, with units having 2 or more layers, the formation of a swollen gel barrier was

320   soon evident during the test. The rate of release decreased as a function of the number of layers. n values

321   showed an increasing trend, thus indicating a shift towards linearity. Accordingly, the linear portion of the

322   release curve from NUDDMat G20-80 (5 layers) ranged from 0.15 to 0.44 of fraction released, and the relevant

323   time frame was 1÷4 h, as assessed by Durbin-Watson statistics. However, an initial phase of higher release
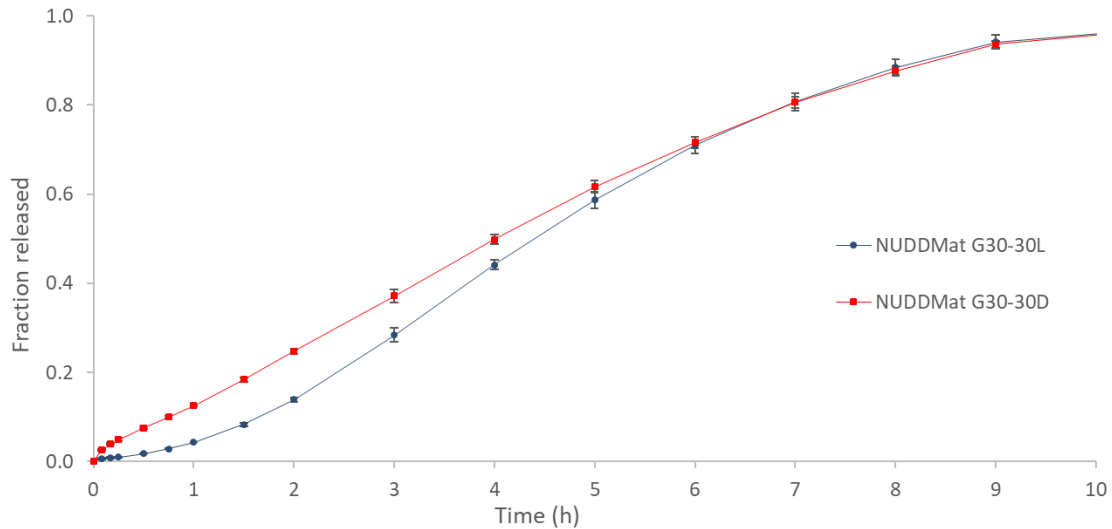
324   rate could still be noticed.

325   Aiming to overcome occurrence of this slight burst, a modified five-layer system, NUDDMat G20-100, was

326   prepared and evaluated. In particular, the 5th layer of NUDDMat G20-100 was devoid of drug tracer, which

327   was replaced by a corresponding amount of HPMC (Table 1). The physical technological characteristics were

328   still satisfactory, and the outermost layer composed of sole polymer turned out effective in suppressing the

329   undesired burst effect (Table 3, Figure 5). However, it brought about a lag time before the onset of release, as

330   testified by n rising up to 1.121 (Table 4). Therefore, the thickness of the outer layer was halved in an attempt

331   to reduce the lag time (NUDDMat G20-100/2), with no impact on mechanical properties was observed (Table

332   3). This system proved useful to solve the lag phase issue and able to yield practically linear release curves

333   (n=0.993) by preventing any burst effect (Figure 5, Table 4). Based on Durbin-Watson statistics, the profile

334   turned out linear from 0.12 to 0.79 of fraction released, between 1 to 7 h.

335   Interestingly, the onion-like structure of NUDDMat systems, which was expected to present concentration

336   steps according to the descending staircase function conceived, was apparently not reflected in the release

337   patterns obtained. Indeed, such steps might have been smoothed through partial migration of the drug tracer

338   upon exposure to the aqueous binding solution during preparation and/or inward diffusion of the aqueous

339   medium during release tests.

340   Because the concentration of HPMC in the NUDDMat systems described so far, of approximately 60%, largely

341   exceeded that usually employed for prolonged-release matrices, the possibility of reducing the overall amount

342   of polymer was explored. Accordingly, systems with polymer content of 30% in all 5 layers, each of 315 µm,

343   were conceived, wherein *i)* the amount of HPMC was increased in the first layer to the detriment of the drug

344   tracer, *ii)* the amount of HPMC was decreased in the other 4 layers through replacement with an insoluble

345   (DCP) and a soluble (lactose) excipient, and *iii)* no drug was loaded into the outer layer. The resulting

346   formulations were named NUDDMat G30-30D and G30-30L, respectively, and the relevant compositions are

347   reported in Table 1. In both cases, slightly improved powder layering processing was noticed, possibly due to

348   the better flowability properties of the diluents as compared with HPMC. The lower amount of polymer was

349   reflected in reduced crushing strenghts, which, however, still remained satisfactory (Table 3).

350   As in previously described NUDDMat systems, the release rate decreased as the number of applied layers

351   increased from all units, either containing DCP or lactose (data not shown). Approximately 80% of drug tracer

was released in 7 h from both NUDDMat G30-30L and G30-30D, in an almost linear mode from the latter system (Figure 6).

Figure 6: release profiles from NUDDMat G30-30L and NUDDMat G30-30D systems.

A slight burst was observed in the relevant curve, even though no drug was contained in the outer layer. This could be attributed to destructuring of the swollen outer polymer layer caused by the dispersed particles of insoluble DCP, here present at the highest concentration of 70%. In contrast, release of the drug tracer from NUDDMat G30-30L was slowed down in the first hour of testing, probably because of soluble lactose bringing about fast formation of an external gel barrier responsible for initially slow diffusion. As shown before for G20-100, this issue could be counteracted by simply reducing the outer layer thickness.

Interestingly, data from NUDDMat G30-30D and G30-30L indicated that partial replacement of the polymer would not impair the overall release control.

367   *Table 3: weight, size, porosity, aspect ratio, crushing strenght and friability of NUDDMat units*

NUDDMat unit	Weight (mg ± s.d.)	Diameter (mm ± s.d.)	Porosity (%)	Aspect ratio (value ± s.d.)	Crushing strenght (N ± s.d.)	Friability (%)
G20-80	43.22±0.34	4.20 ±0.13	5.73	1.05 ± 0.04	204 ± 23	0.42
G20-100	40.36 ±0.29	4.11 ±0.12	6.47	1.06 ± 0.03	165 ± 17	0.01
G20-100/2	33.89 ±0.41	3.87 ±0.14	6.16	1.07 ± 0.04	170 ± 15	0.02
G30-30L	49.43 ±0.68	4.26 ±0.21	5.59	1.02 ± 0.02	125 ± 10	0.33
G30-30D	58.05 ±0.79	4.13 ±0.16	7.35	1.03 ± 0.02	146 ± 8	0.13

368

369

370   *Table 4: release parameters according to exponential equation (2)*

|	n	confidence interval 95%	k	R^2
UDDMat T30	0.832	0.061	0.229	0.989
UDDMat P30	0.775	0.056	0.271	0.981
1-layer unit	*	*	*	*
2-layer unit	0.662	0.001	1.719	0.876
3-layer unit	0.671	0.002	1.490	0.984
4-layer unit	0.732	0.003	1.305	0.999
NUDDMat G20-80	0.756	0.025	1.190	0.999
NUDDMat G20-100	1.121	0.002	0.067	0.915
NUDDMat G20-100/2	0.993	0.002	0.123	0.940
NUDDMat G30-30L	1.227	0.003	0.809	0.986
NUDDMat G30-30D	0.802	0.003	1.184	0.997

371   *- Not applicable

372

373   *Raman mapping analysis*

374   In order to highlight the drug and polymer distribution throughout the layered formulations, it was deemed

375   interesting to perform imaging analyses by Raman mapping microscopy. The distribution of the drug tracer

376   particles within layered matrices was evaluated on cross-sectioned UDDMat P30 and NUDDMat G30-30D

377   systems. The mapping was performed by assigning false colors to AAP, HPMC (or cellulose), DCP and to the

378   AAP/HPMC ratio after identification of specific peaks of the spectra (Figure 7). Although no HPMC was

379   contained in the seed formulation, quite a strong blue signal was highlighted, because cellulose, namely MCC,

380   was present as the main component.

381

	AAP	HPMC	DCP	AAP/HPMC ratio
UDDMat P30			-	
NUDDMat G30-30D				
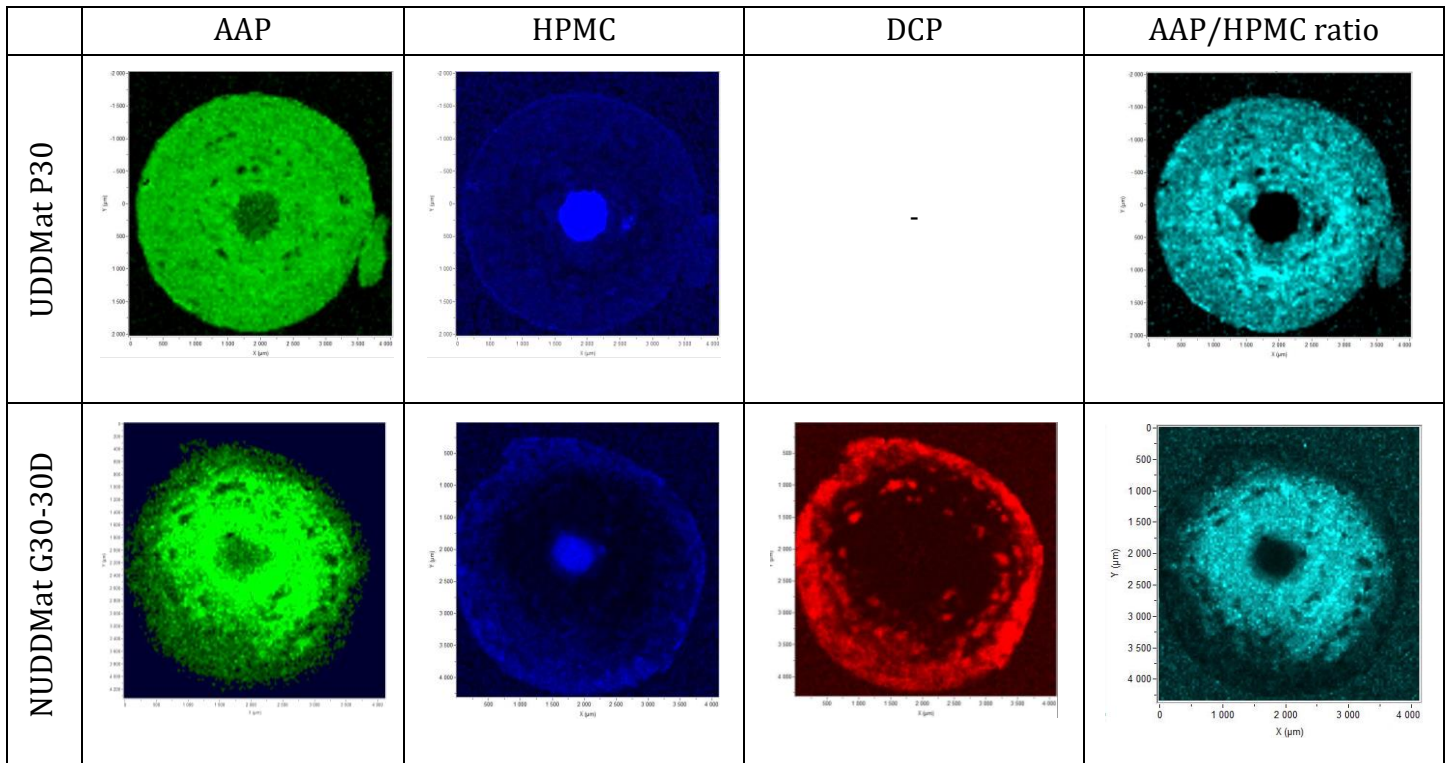
382

383 *Figure 7: Raman mapping microscopy images relevant to AAP, HPMC, DCP and AAP/HPMC ratio acquired from*
384 *cross-sectioned UDDMat P30 and NUDDMat G30-30D systems. Mapping refers to areas of approximately 4000 x*
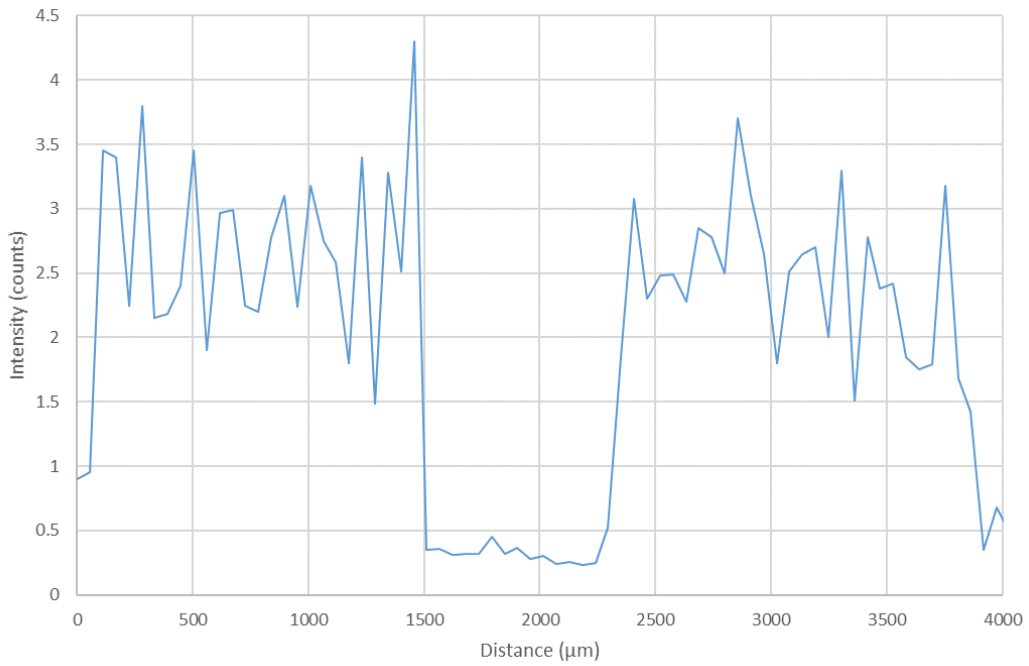385 *4000 μm.*

386

387 The color intensity of AAP/HPMC ratio was plotted along the diameter of the cross-sectioned units (Figure
388 8).
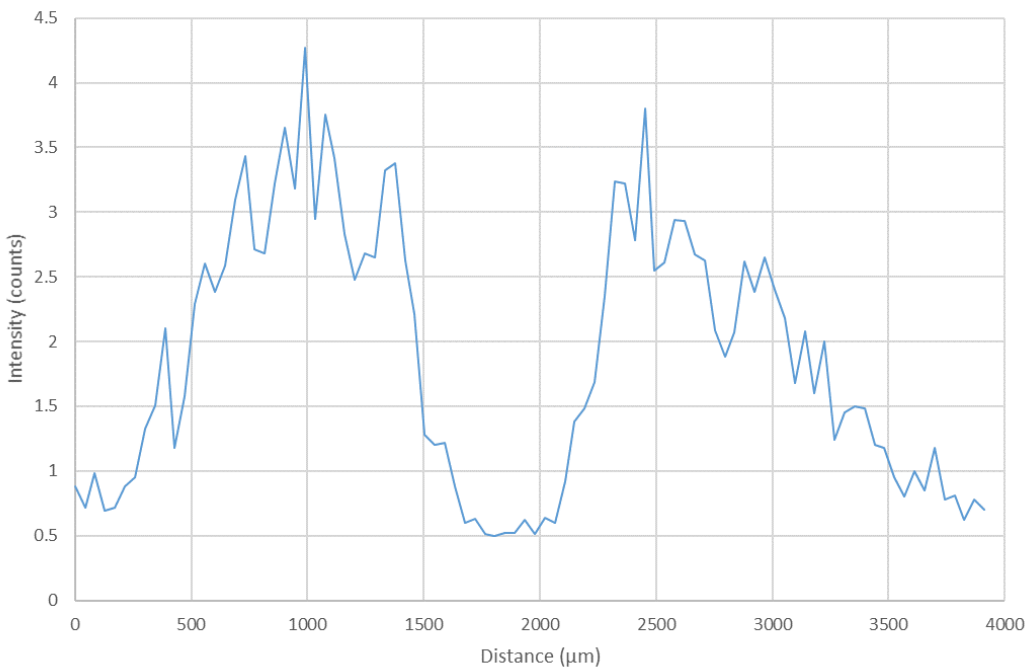
389

390

391   a)

392

393   b)

394

395   *Figure 8: profiles of AAP/HPMC ratio calculated from Raman mapping microscopy images along the diameter of*
396   *cross-sectioned UDDMat P30 (a) and NUDDMat G30-30D (b) systems*

397

398 In the UDDMat P30 system, the AAP/HPMC intensity ratio profile, calculated along one diameter, suggested
399 a uniform concentration of AAP throughout the layered powders and pointed out the sole presence of cellulose
400 in the seed core (Figure 8 a). For NUDDMat G30-30D, a gradient of AAP/HPMC intensity ratio indicated a
401 non-uniform concentration of drug tracer, decreasing from the inside to the outside of the unit. Particularly, a
402 rise towards the center and a steep fall close to the core, devoid of drug, were highlighted, exactly matching
403 the 3D hyperspectral map (Figure 8 b, Figure 9). The lack of a staircase concentration pattern, previously
404 hypothesized from the evaluation of the release curves, seemed to be confirmed by the AAP/HPMC intensity
405 ratio profile.

406
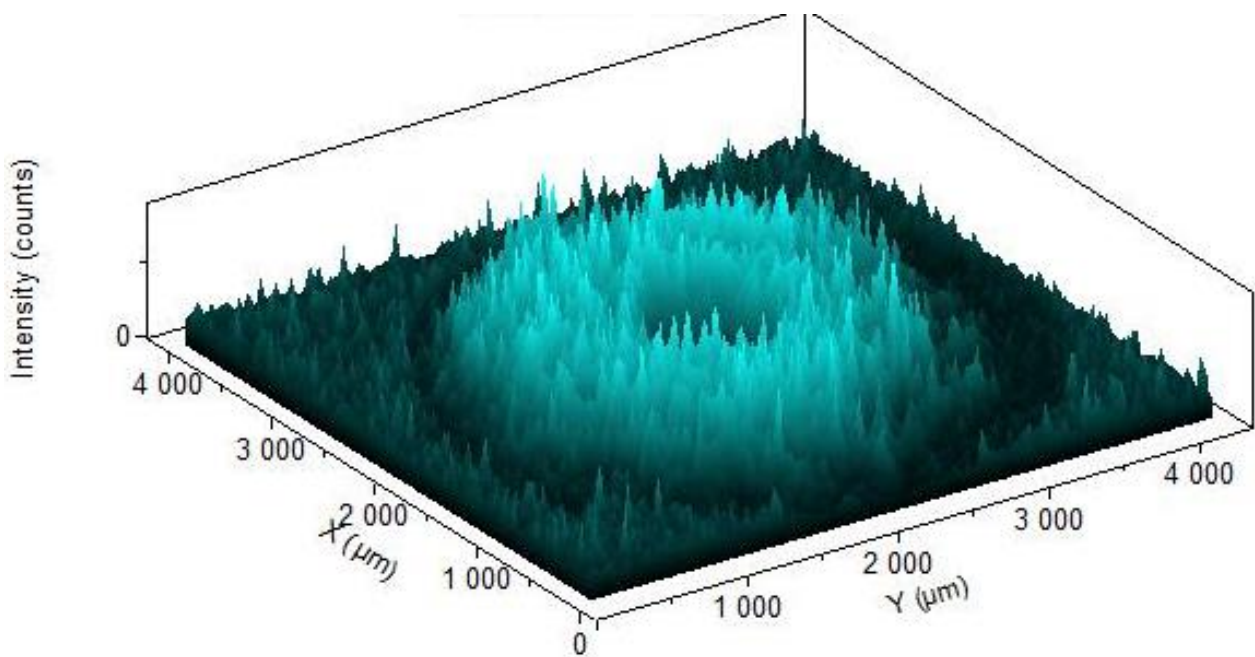
407

408

409 *Figure 9: hyperspectral 3D mapping by Raman microscopy relevant to color intensity of AAP/HPMC ratio acquired*
410 *from a NUDDMat G30-30D system. Mapping refers to areas of approximately 4000 x 4000 μm.*

411

412

413 **CONCLUSIONS**

414 A hydrophilic matrix system intended for zero-order release was designed and fabricated by subsequent
415 deposition onto inert cores of layers having outwards decreasing drug concentrations. For this purpose, the use
416 of powder layering was explored, which offers major advantages because of the small amount of solvents
417 involved and reduced costs as compared with other layering techniques. Spherical units of 4 mm in diameter
418 were thereby obtained, exhibiting satisfactory physico-technological characteristics. The non-uniform
419 composition of the layered matrix, varying along its cross-sectional axis, was highlighted by Raman mapping
420 analysis. The particular configuration of NUDDMat was demonstrated to reduce the initial burst effect typical

of hydrophilic matrices, which, as expected, was yielded by a formulation having equal overall composition though uniform drug distribution. Moreover, this configuration proved effective in contrasting other drawbacks that are associated with hydrophilic matrices, such as the lengthening of the diffusional pathway and reduction of the area at the swelling front, both responsible for a progressive decrease in the release rate. The desired zero-order release profiles were thus obtained from the NUDDMat system, as confirmed through Durbin-Watson statistics that pointed out extension of the linear portion of release curves.

As regards drug loading, the NUDDMat technology proposed would in principle not differ from classical hydrophilic matrix systems. Actually, based on the NUDDMat G20-100/2 formulation yielding zero-order release, which already contained around 33% of tracer, drug content higher than 50% could be achieved. The percentage of polymer could indeed be reduced in the innermost layers provided that in the outer one it is maintained at least in a 20-30% range, needed to ensure matrix structure formation upon glassy-rubbery transition. The simple design concept of the novel gradient composition matrix and the use of a more advantageous technique as compared with previous attempts reported in the literature make the delivery platform hereby proposed a valuable strategy to improve the performance of hydrophilic matrix systems for prolonged release.

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