Cushion-coated pellets for tableting without external excipients

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ABSTRACT

Multiple-unit pharmaceutical dosage forms prepared by compacting pellets offer important biopharmaceutical and compliance advantages over formulations obtained by filling capsules as they enable more convenient dose adaption and easier swallowing. However, pellet compaction may negatively affect the release control mechanism, and subunits may not be readily available in individual form once administered. Aiming to avoid the use of mixtures of pellets and excipients to promote compaction and limit the impact of the forces involved, the application of a layer having cushioning function to the starting units is here proposed as a strategy to obtain tablets with satisfactory mechanical strength, rapid disintegration, and maintenance of the expected release profile of the individual subunits. Gastro-resistant pellets having an outer layer of PEG1500, a soft and soluble material, were shown to consolidate after the application of relatively low compaction pressures, which allowed to maintain their inherent release performance after tablet disintegration. Adhesion problems associated with the use of PEG1500 were overcome by applying an outer film of Kollicoat® IR. Through implementation of a design of experiment (DoE), the robustness of the proposed approach was demonstrated and the formulation and as well as tableting conditions were optimized.

1. Introduction

Multiple-unit pellet systems (MUPSs), compared with single-unit dosage forms, offer several types of advantages. Less variability in gastric residence time is fundamentally reflected in greater reproducibility of transit time throughout the entire gastrointestinal tract, resulting in better performance in terms of extent and rate of absorption of the active ingredient (Bhad et al., 2010; Chen et al., 2017; Majeed et al., 2020). MUPSs show great flexibility in formulation design and, therefore, allow fine tuning of the release profile (Abdul et al., 2010; Di Pretoro et al., 2010). Indeed, they have been exploited in oral drug delivery to attain control of the release in terms of rate, time and site within the gastrointestinal tract (Cerea et al., 2018; Del Curto et al., 2011; Gazzaniga et al., 2022; Maroni et al., 2016, 2013; Moutaharrik et al., 2023; Palugan et al., 2015; Schultz et al., 1997; Schultz and Kleinebudde, 1997). They also have improved safety characteristics because of a broader distribution of units along the gastrointestinal tract reducing the risk of local mucosal damage and dose-dumping. Finally, pellet dosage forms have technological advantages over granulated formulations due to their smoother surface, higher mechanical strength and narrower particle size distribution, which could lead to more uniform coating thickness and better flow properties.

The manufacturing of MUPSs can be done by filling into capsules or by tableting (Breitkreutz, 2005; Reddy et al., 2011; Santos et al., 2005; Sawicki and Łunio, 2005). Capsule preparation is generally considered simpler, as the risk of compromising the integrity of the pellets is avoided. However, the use of capsules could be associated with lower patient compliance: capsules are in fact larger in size than the corresponding tablets, which could cause problems with swallowing and adhesion to the mucosa during transit throughout the esophagus. Moreover, tableting of pellets would provide a faster and less expensive process, and the manufacturing of tablets with scored lines could also allow easier splitting for dose adjustment. However, tableting of pellets involves multiple challenges, primarily involving mass and content uniformity issues (Bodmeier, 1997; Chen et al., 2017). Moreover, it is necessary to obtain tablets with adequate mechanical strength and to ensure that the structural integrity of the pellets is maintained, as well as their functionality (*i.e.*, drug release profile). The tableted MUPSs are expected to disintegrate rapidly, so that each subunit can transit along the gastrointestinal tract independently. When dealing with reservoir-type pellets, the coating applied has to withstand the compaction pressure; it may deform but cannot break as the presence of cracks in the film would impact on the drug release performance (Thio et al., 2022). The mechanical characteristics of the coating are related to its thickness, the type of polymer, the type and amount of plasticizer and the curing phase (Bando and McGinity, 2006; Bashaiwoldu et al., 2011).

The main strategy to avoid damage to the starting pellets when they are subjected to tableting and to have a prompt disintegration of the resulting dosage form involves the use of cushioning excipients previously mixed with or, in few cases, layered on the surface of the subunits (Abdul et al., 2010; Chen et al., 2017; Hosseini et al., 2013; Sántha et al., 2021). To reduce the risk of deformation, breakage or fusion of the original pellets, the proposed excipients are typically selected among those having good compaction properties,

which would ultimately limit any direct contact of the units with each other while allowing for rapid disintegration of the tablet (Csobán et al., 2016; De Alencar et al., 2017; Gómez-Carracedo et al., 2008; Stange et al., 2013). The pellet-to-excipient ratio is an important parameter that influences the mechanical strength, disintegration time, mass and drug content uniformity of the resulting tablets, as well as the integrity of the tableted subunits (Bianchini et al., 1992; Debunne et al., 2004; Pinto et al., 1997a, 1997b). To address the risk of segregation in the mixtures of pellets and cushioning excipients, the use of fillers with a relatively large particle size or of *placebo* pellets was proposed, meeting most of the desired requirements (Beckert et al., 1998; Elsergany et al., 2020; Lundqvist et al., 1998; Lundqvist and Podczeck, 1997; Sántha et al., 2021; Wagner et al., 1999).

Numerous approaches to overcoming the problem of damages to functional pellet coatings consisted in modifying the coating formulation with the addition of materials absorbing the applied compaction forces, as in the case of the Eudragit NE30D used to improve the elongation at break properties of Eudragit L 30 D55 (Beckert et al., 1996; Dashevsky et al., 2004). However, it was observed that such modifications often altered the release control ability of the films, hindering their functionality. To avoid mixing of the starting pellets with fillers and possible segregation during tableting, the application of shock-absorbing layers (cushion) composed of excipients with good compaction properties to the pellet surface was proposed. Altaf and coauthors described the use of microcrystalline cellulose or mannitol applied to pellets provided with prolonged-release ethyl cellulose membranes alternating with layers of model drug acetaminophen (Altaf et al., 1998). When pellets coated with approximately 80% w/w of microcrystalline cellulose were employed, segregation of mixed cushioning excipients was ruled out. However, the resulting tablets turned out physically weak due to the larger size of the starting pellets. Since high tableting pressures were required, deformation of the pellets and total loss of sustained release properties were also observed. Husseini and coauthors described a process based on the layering onto ethyl cellulose-coated pellets of an ethanolic suspension containing a filler, a disintegrant and optionally a glidant (Hosseini et al., 2013). Microcrystalline cellulose, lactose or sorbitol were evaluated as the filler, croscarmellose sodium as the superdisintegrant, and magnesium stearate or sodium stearyl fumarate as the glidant. Polyvinyl pyrrolidone (PVP) was selected as the best binder during suspension layering also avoiding disintegration issues of the tablets. Osei-Yeboah and coauthors used the same polymer (PVP K30) for the application of a single cushioning layer to pellets coated with Kollicoat MAE (40% w/w) (Osei-Yeboah et al., 2017). Prior to tableting, the cushioned pellets were stored at different relative humidity (RH) conditions in order to provide a more plasticized PVP layer that could form larger bonding areas under compaction. Thicker PVP layers and higher RH conditions resulted in stronger tablets. However, in these conditions intimate bonding among adjacent pellets and flowing (caking) problems arose, requiring the addition of 1% w/w fumed silica to the cushioning layer to enhance flowability. This approach imparted good compaction properties to the pellets while leading to only minor alteration of the release profiles.

In the development of a MUPS by tableting of coated pellets, not only the core, coating composition and the cushioning excipient characteristics have to properly be selected, but also the compression parameters need to be taken into account, particularly with regard to compression force, tableting speed, tooling design and powder feeder type (Karolak et al., 2020; Vasiljević et al., 2021; Xu et al., 2016).

In this work, a new formulation strategy to convey modified-release pellets into tablets without the need for mixing with external cushioning excipients is proposed. Thanks to a special design involving an outer layer of a soft and soluble material, compaction of the individual units under low pressures would be possible, along with maintenance of their inherent release performance after tablet disintegration. To prove the validity of this approach, the design of PEG1500-coated gastro-resistant units and the relevant tableting conditions were defined and optimized through the application of Design of Experiment (DoE).

2. Materials

Sugar spheres 20/25 mesh (Surinerts®) were kindly gifted by IPS (International Products & Services, San Donato Milanese, IT); sodium laurylsulfate (Kolliphor®, SLS), polyvinylpirrolidone (Kollidon® 30, PVP), polyvinyl alcohol and poly ethylene glycol co-polymer (Kollicoat® IR, KIR) and methacrylic acid and ethyl acrylate copolymer, in 30% w:w suspension (Kollicoat® MAE 30DP) were kindly gifted by BASF (Ludwigshafen, DE); polyethylene glycol 1500 (Polyglykol® 1500, PEG1500) was kindly gifted by Clariant (Muttenz, CH) and hypromellose (Methocel™ E5, HPMC E5) by Colorcon (Dartford, UK). Acetaminophen fine powder EP (AAP, Rhodapap™) was purchased from Novacyl (Lyon, F), talc and propylene glycol (PG) from ACEF (Fiorenzuola d'Arda, IT).

3. Methods

3.1 Manufacturing and characterization of pellets

Manufacturing of pellets involved the deposition of acetaminophen (AAP) as a tracer drug (Giordano et al., 2002) and of successive coating layers starting from sugar spheres with particle sizes in the 710-850 µm range. The composition of the liquid formulations used to deposit each layer is shown in Table 1, whereas equipment and processing conditions are reported in Table 2. Various types of units were prepared according to the different layers applied, as identified by codes listed in Table 3.

Table 1. Composition of the formulations employed for application of drug and successive coating layers onto sugar spheres

	Layer				
	Drug	**Gastro-resistant**	**Isolating**	**Cushioning**	**Anti-sticking**
Component	Amount % (w/w)				
AAP	8.0	-	-	-	-
SLS	0.5	-	-	-	-
PVP	3.5	-	-	-	-
Kollicoat® MAE 30DP	-	50.0	-	-	-
PG	-	4.5	-	-	-
Methocel®E5	-	-	8.0	-	-
PEG1500	-	-	-	50.0	-
Kollicoat® IR	-	-	-	-	15.0
Talc	-	4.0	-	-	3.0
Demineralized water	88.0	41.5	92.0	50.0	82.0

All the formulations were prepared by dissolving/dispersing the solid components in demineralized water at room temperature under continuous magnetic stirring. For the preparation of the enteric coating dispersion, talc and PG were pre-mixed with Kollicoat® MAE 30DP under continuous magnetic stirring and then water was added.

Table 2. Process equipment and conditions employed for application of drug and successive coatings onto sugar spheres

	Tracer drug	**Gastro-resistant**	**Isolating**	**Cushioning**	**Anti-sticking**
Equipment type	*Rotor tangential-spray fluid bed#*	*Wurster bottom-spray fluid bed#*	*Wurster bottom-spray fluid bed#*	*Wurster bottom spray fluid bed§*	*Wurster bottom spray fluid bed§*
	Process parameters				
Inlet air flow (m^3/h)	65	65	55	8.6	15
Inlet air temperature (°C)	50	55	50	20	20
Outlet air temperature (°C)	30	36	35	-	-
Product temperature (°C)	38	43	40	15	19
Nozzle diameter (mm)	1.2	1.2	1.2	0.5	0.5
Spray pressure (bar)	2.0	2.0	2.0	1.0	1.0
Liquid flow (g/min)	7.0-8.0	6.0 – 7.0	2.0 – 3.0	0.4 – 0.6	0.2 – 0.4
Rotor speed (rpm)	400	-	-	-	-
Drying phase duration (min)	10	5	5-10	5	5
Drying inlet air temperature (°C)	50-55	55	55	20	20
Amount of starting substrates (g)	1000	400	400	50	50
Liquid formulation added (g)	1000	1333	800	206/275/343*	33/66*

#GPCG 1.1 and §Miniglatt (Glatt, Binzen, DE)

**different amounts depending on the required coating level*

Table 3. Codes identifying the types of individual units and tableted MUPS manufactured

Code	Sample type	Coating(s) applied onto drug-layered cores			
		Gastro-resistant	Isolating	Cushioning	Anti-sticking
uU	individual units	-	-	-	-
uG	individual units	X	-	-	-
uGI	individual units	X	X	-	-
$uGC_{\%}$	individual units	X		X	-
$uGIC_{\%}$	individual units	X	X	X	-
$uGIC_{\%}A_{\%}$	individual units	X	X	X	X
tG	tableted units	X	-	-	-
tGI	tableted units	X	X	-	-
$tGIC_{\%}$	tableted units	X	X	X	-
$tGIC_{\%}A_{\%}$	tableted units	X	X	X	X

% indicates nominal weight gain due to application of PEG1500 and of KIR onto the relevant substrates

Actual percentage weight gained after each layering step was calculated from the weight of 200 units collected before (w_{n-1}) and after (w_n) each coating step (E 50 S/3 Gibertini, Novate Milanese, IT), according to eq. 1.

$$wg_{\%} = \frac{(w_n - w_{n-1})}{w_{n-1}} * 100 \quad (1)$$

Process yield (Y%) was calculated after each coating step from the actual weight gain and the theoretical one, the latter being inferred from the total amount of coating material employed in that coating step.

The final pellets were stored in polythene bags at ambient conditions (15-21°C temperature range).

Shape and size of units obtained after each layering step were evaluated through photographic images taken by a digital microscope connected to a software (Dino-Lite Pro AM 413T and Dino-Lite Pro 2.0, AnMo Electronics Corporation, New Taipei City, TW). The images were analyzed using ImageJ software (National Institutes of Health, 1.53b 2020, Bethesda, US-MD) to measure the projected area (A) of individual units (*n*=30), from which the equivalent spherical diameter area (d_A) was calculated according to eq. 2:

$$d_A = 2 * \sqrt{A/\pi} \quad (2)$$

The mean equivalent spherical diameter area of the units obtained after a given coating process ($\overline{d}_{A_n}$) and that of the starting substrates (*i.e.* units after a previous layering step, $\overline{d}_{A_{n-1}}$) were then used to calculate the thickness of the applied layer (t_n) according to eq.3:

$$t_n = \frac{\overline{d}_{A_n} - \overline{d}_{A_{n-1}}}{2} \quad (3)$$

The amount of material layered per unit area after each layering step was calculated from the mass of the starting substrates, the actual % weight gain attained with the layering step and the mean diameter of the substrates.

Morphology of the units was investigated using Scanning Electron Microscope (SEM-Zeiss EVO MA10 (Carl Zeiss, Oberkochen, DE). Gold-sputtered samples were observed by SEM under vacuum at different magnifications.

Release test was carried out according to Eur. Ph. 11.4, monograph 2.9.3, method B for delayed-release dosage forms. An amount of pellets corresponding to that of tableted MUPS (400 or 680 mg) was tested in compendial apparatus 2 (AT7, Sotax, Aesch, CH) using 900 mL of HCl 0.1 N thermostated at 37.0±0.5 °C and under a paddle rotation speed of 100 rpm. After 2 h, the medium was replaced with phosphate buffer pH 6.8. The amount of AAP released was measured by a UV spectrophotometer (Lambda 35, Perkin Elmer Italia, Monza, IT; 1 mm cuvette, λ = 248 nm).

3.2 Manufacturing and characterization of tableted MUPS

Tableting of pellets was performed by a rotary tablet press (AMS8, Officine Meccaniche Ronchi, Cinisello Balsamo, IT) equipped with flat-faced 11 mm punches or concave punches having oblong 20x8 mm shape to obtain tablets of 400 mg or 680 mg nominal mass, respectively. Samples of pellets were weighed (Crystal 500, Gibertini, Novate Milanese, IT), manually filled into the die and tableted at a rotating turret speed of 20 rpm.

The force at upper punch (F_a) was measured for each tablet (FIT 2008 Technology, B&D Italia, Carate Brianza, IT) (*n*=30). The obtained tablets were packaged in PVC blisters and stored under ambient conditions. They were characterized for mass (Crystal 500 analytical balance) and dimensions (Carbon Fiber Digital Caliper ref.10745, Metrica, San Donato Milanese, IT; *n*=6). Resistance to handling of cylindrical tablets was assessed by placing them on a stainless-steel sieve with 500 µm mesh openings, which was subjected to automated mechanical shaking (sieve shaker Retsch AS200 basic, Haan, DE, operating at the maximum amplitude). After 3 min, the units underwent visual inspection and were evaluated for integrity (*i.e.* no breakage or mass detachment) (*n*=6).

Tensile strength (TS) of oblong tablets was determined according to eq. 4:

$$TS = \frac{2}{3}\left(\frac{10P}{\pi D^2\left(2.84\frac{t}{D} - 0.126\frac{t}{W} + 3.15\frac{W}{D} + 0.01\right)}\right) \qquad (4)$$

where P is the fracture load, D is the length of the tablet, t is the overall thickness and W is the wall height of the tablet (Pitt and Heasley, 2013). Fracture load was measured along the longer axis of the tablet by means of a Texture Analyzer (TA.XT plus, Stable Micro Systems, Godalming, UK). Measurements were performed in triplicate.

Disintegration test was performed in compendial apparatus (DT3, Sotax, Aesch, CH) using 800 mL of demineralized water thermostated at 37.0±0.5 °C. The time to disintegration (t_{dis}) was recorded as the time after which only individual pellets were observed (*n*=3).

Release test was carried out according to Eur. Ph. 11.4, monograph 2.9.3, method B for delayed-release dosage forms. Tablets (400 or 680 mg) and corresponding amounts of pellets were tested in compendial apparatus 2 (AT7, Sotax, Aesch, CH) using 900 mL of HCl 0.1 N thermostated at 37.0±0.5 °C under a paddle rotation speed of 100 rpm. After 2 h, the medium was replaced with phosphate buffer pH 6.8. The amount of acetaminophen released was measured by a UV spectrophotometer (Lambda 35, Perkin Elmer Italia, Monza, IT; 1 mm cuvette, λ = 248 nm).

SEM analysis and release test were performed as described for the characterization of individual units.

3.3 DoE and statistical analysis of the results

Results obtained from the tests conducted according to design of experiments (DoE) were analyzed by MiniTab 18 software (GMSL, Nerviano, IT). Regression and correlation coefficients of the mathematical models, their significance values and the desirability function were calculated.

4. Results

4.1 Rationale and formulation design of subunits for tableted MUPS

In this work, a new formulation approach is proposed for the preparation of tableted MUPS consisting of modified-release subunits. Specifically, the overall design of the starting subunits includes an outer cushioning layer that should promote the formation of a coherent (mechanically resistant) tablet when the individual units are subjected to relatively low compaction forces. In this way, the risk of loss of integrity and, therefore, of functionality of the modified-release units due to the mechanical stress associated with tableting could be reduced, and the original multiple units could be restored after tablet disintegration upon contact with aqueous fluids. In principle, this "cushioning" layer should work for different types of pellets, *i.e.* matrix or reservoir, regardless of the relevant composition, thus representing a versatile approach to manufacturing of tableted MUPSs (Figure 1).

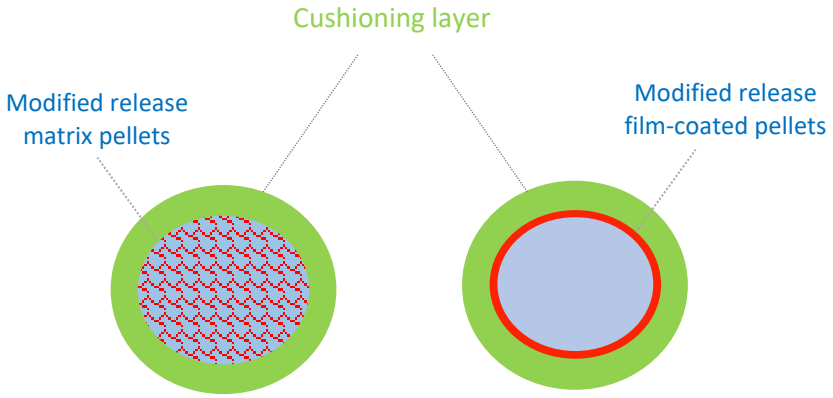

Figure 1. Outline of different types of cushion-coated units intended for tableted MUPSs.

Inspired by pioneering papers on the role of PEGs in pellets and tablets formulation, these polymeric materials, having soft nature and hydrophilic character, were identified as potentially suitable for the formation of the cushioning layer (Larhrib et al., 1997; Larhrib and Wells, 1997)(Nicklasson and Alderborn, 1999). PEG1500 was specifically chosen among the different molecular weight grades available in view of its high solubility and low melting temperature range (44-48 °C), which was expected to promote consolidation of the units on the one hand, and rapid disintegration following exposure to aqueous fluids on the other. In order to evaluate the ability of PEG to preserve the integrity of pellets in compaction, units containing a tracer drug (AAP) provided with a gastro-resistant film were used as challenging model substrates. Indeed, acrylic enteric coatings, specifically consisting of 1:1 methacrylic acid-ethyl acrylate copolymer, are known to be

susceptible to possible mechanical damages resulting from tableting, being particularly brittle even when purposely plasticized (Dashevsky A. et al., 2004).

Several exploratory tests were carried out to set up the coating conditions for stratifying PEG1500 onto gastro-resistant units as provided by the design concept. Then, the units were evaluated for compaction properties, using Ø11mm flat-faced punches and testing the obtained compacts for hardness, disintegration and release performance.

Primary cores were prepared by layering onto inert seeds an aqueous suspension of AAP, also containing SLS and PVP to increase wettability and adhesion of the drug particles, respectively. This technique was preferred to other manufacturing methods as it allows excellent characteristics to be achieved in terms of size distribution and sphericity of the units. Such properties, in principle, should reduce the influence of factors other than the cushioning layer formulation on the tableting outcome. Sugar spheres in the 710-850 µm size range were loaded with AAP to approximately 6% w.g..

Drug-layered units were then coated with MAE up to a nominal thickness of 35 µm, corresponding to about 12 mg/cm^2 and 30% weight gain. This film was effective in yielding gastro-protection, *i.e.* it was able to prevent leakage of the tracer in the acidic stage of the release test, then allowing its rapid and complete release in buffer medium pH 6.8. Nonetheless, tableting of these film-coated units into coherent compacts required relatively high forces (13 kN), which led to the loss of gastro-resistant properties (Figure 2).

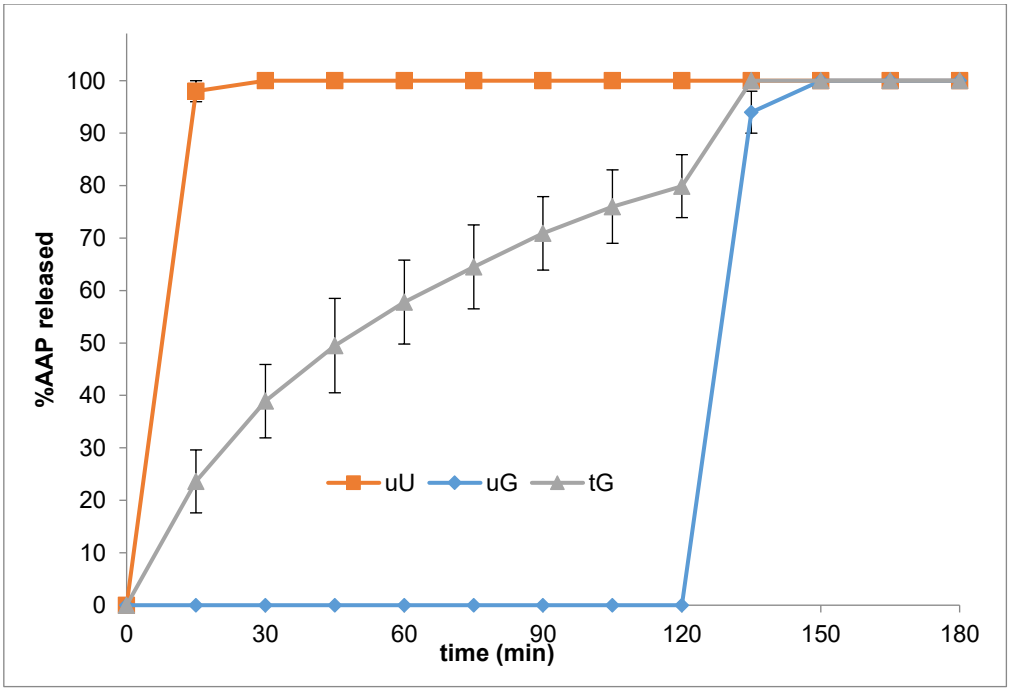

Figure 2 Release profiles of AAP from individual uncoated units (uU), gastro-resistant units (uG) and tableted gastro-resistant units (tG).

The gastro-resistant units (uG) were then provided with the cushioning layer by spraying an aqueous solution of PEG1500 up to a weight gain of 50%. The coating operations posed critical issues related to the stickiness

of PEG1500 that involved maintaining the process temperature sufficiently low (20 °C) to avoid the formation of aggregates (multiples). Samples collected at different coating levels, tested immediately after preparation, were shown to meet gastro-resistance requirements. Nonetheless, within few days they tended to turn yellow and lose gastro-protection ability, suggesting a possible plasticizing effect of PEG1500 towards the acrylic resin that would impair the effectiveness of the coating in controlling drug release (Breitkreutz, 2000). Therefore, a separation film between the gastro-resistant and cushioning layers was added. Hypromellose, being commonly employed as sealing film-forming polymer in coating processes, was used to this aim (Ishibashi et al IJP1998, JPS1998). In detail, MAE-coated units were spray-coated with a solution of a low viscosity and soluble HPMC grade (Methocel® E5) to achieve a thin film, corresponding to approximately 5 mg/cm^2 of polymer applied.

The resulting units were further coated with PEG1500 in increasing amounts (10, 20, 30, 40 and 50% w.g.), thus yielding the cushioned units (Table 4). These presented spherical shape and rather smooth surface (Figure 3), narrow size distribution and consistent gastro-protection properties (Figure 4), that in this case were maintained over time (data not shown).

Table 4. Physico-technological characteristics of PEG1500-cushioned units and corresponding tablets

PEG-coated units			Tablet			
code	Weight gain %	Thickness (µm)	Code	Fa (kN) *mean±sd*	Disintegration time (min) *mean (CV<10)*	Gastro-resistance test
$uGIC_{10}$	13.01	21	$tGIC_{10}$	0.69±0.16	3.5	failed
$uGIC_{20}$	21.12	30	$tGIC_{20}$	0.68±0.14	5.4	failed
$uGIC_{30}$	28.64	51	$tGIC_{30}$	0.67±0.08	8.0	passed
$uGIC_{40}$	40.70	62	$tGIC_{40}$	0.70±0.07	9.7	passed
$uGIC_{50}$	47.71	71	$tGIC_{50}$	0.68±0.08	9.7	passed

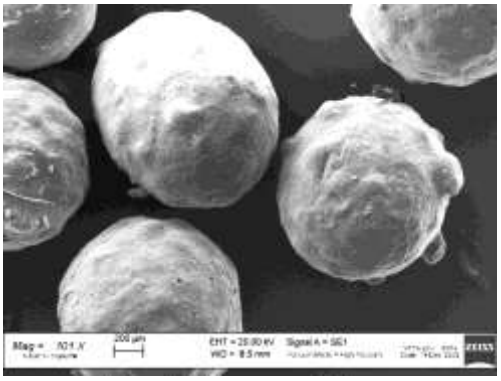

Figure 3. SEM photomicrographs of units coated with PEG1500 to 50% w.g. ($uGIC_{50}$).

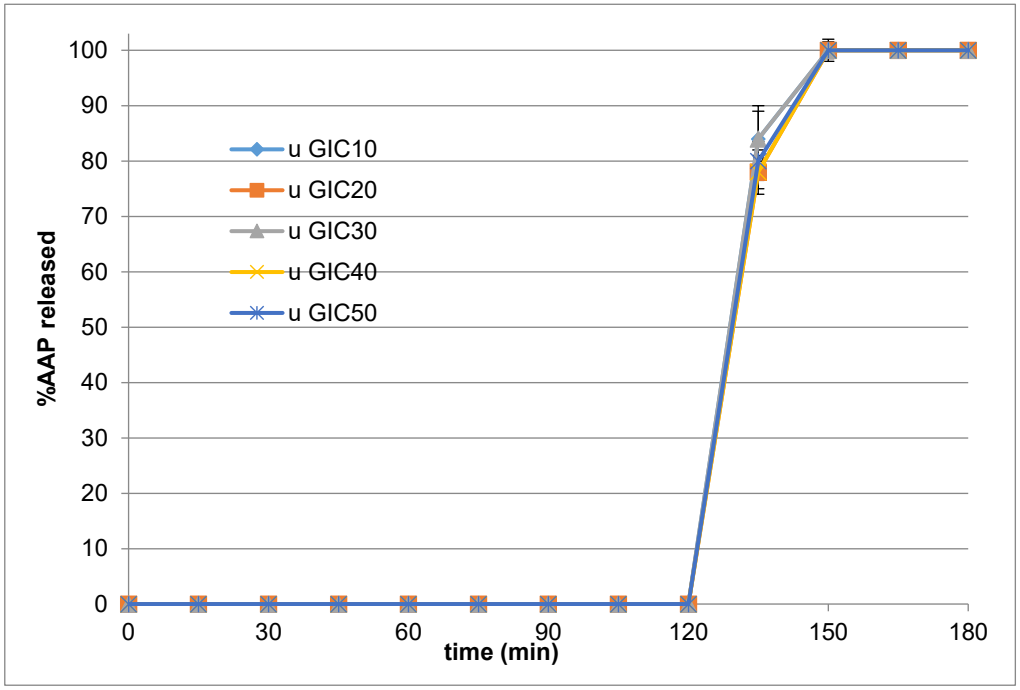

Figure 4. Release profiles of AAP from individual gastro-resistant units coated with PEG1500 to 10-50% weight gain.

Tableting of the cushioned units was carried in a rotary machine, equipped with flat-faced round 11mm punches, filling the die manually and rotating the turret at 20 rpm. Relatively low forces, <100 N, were found sufficient to obtain tablets able to withstand gentle handling. When tested for crushing strength according to compendial monograph, these tablets did not actually break but rather underwent progressive deformation. Despite this, they proved capable of resisting the mechanical stress they were subjected to when placed inside a shaken sieve.

All the obtained tablets showed satisfactory disintegration time, which seemed to increase with the extent of cushioning. Moreover, units coated with PEG1500 to 30% w.g. or higher passed the compendial test to assess gastro-resistance (Figure 5). Therefore, a threshold thickness value seemed to be necessary for the PEG layer (higher than 30 µm) to protect the MAE film, absorbing the impact of compaction through possible deformation.

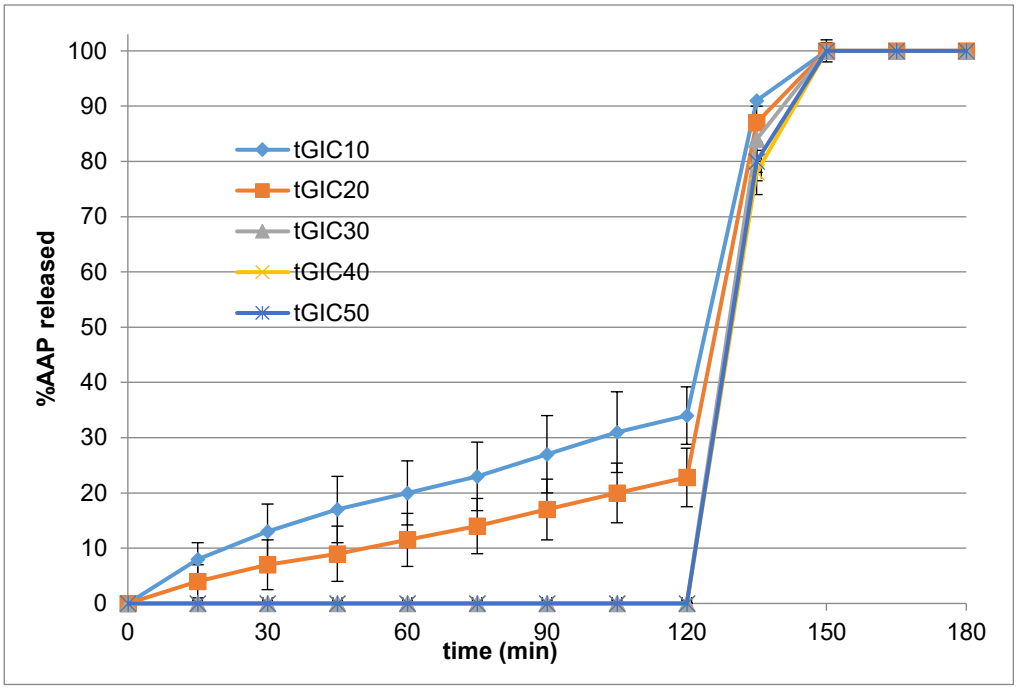

Figure 5. Release profiles of AAP from tableted gastro-resistant units cushion-coated with PEG1500 to different weight gains.

Stored under ambient conditions, individual PEG-coated units and the corresponding tablets showed a slight tendency to adhere to each other and to the inner walls of polythene bags, and to PVC blisters, respectively. To address this issue, an outer film having anti-sticking properties was applied. Particularly, PVA/PEG co-polymer (Kollicoat® IR, KIR) was loaded onto more challenging uGIC50 substrates up to 10% w.g., approximately corresponding to 20 µm and 2 mg/cm^2, proving effective in reducing the observed sticking problems without affecting the release performance.

Therefore, the final design of these cushion-coated pellets resulted in a multilayer structure as outlined in Figure 6.

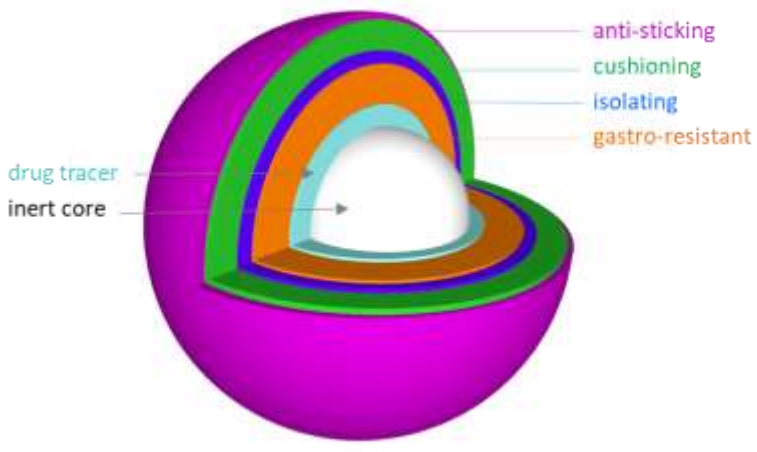

Figure 6. Schematic of the final multilayer cushioned units

4.2. Evaluation of factors affecting the properties of tableted MUPS through application of DoE

Based on the results obtained so far, further studies were carried out to assess the influence of the main formulation and manufacturing factors on the properties and performance of the tableted MUPS.

In this phase of the work, a different set of die and punches was employed so that oblong convex tablets 2 cm long could be obtained, suitable for conveying a greater amount of pellets (680 mg) as compared with the previously manufactured cylindrical one. In more detail, this part of the study was aimed at investigating the robustness of the overall formulation design proposed to obtain tableted MUPS and assessing the experimental space within which the involved factors could be varied to have tablets of acceptable quality.

Particularly, the influence of (a) the amount of cushion-coating ($WG\%_C$), (b) the amount of anti-sticking coating ($WG\%_A$) and (c) the compaction force (F_a) on properties of the tablets, such as resistance to handling, disintegration time and release performance was investigated. The amount of cushion coating was set to three levels of theoretical % weight gain with respect to the starting gastro-resistant cores (uGI). Based on results of the previous phase of the work, 30% was chosen as the minimum weight gain to be reached for the cushioning layer, while 50% was maintained as the highest weight gain in order to rule out a greater impact on the final weight of the units. The anti-sticking coating was set to 5 and 10% w.g. The latter, in fact, was proved to avoid problems of adhesion of pellets and tablets to each other or to the packaging during storage. The lower level of 5%, corresponding to an amount of KIR per unit area between 1 and 2 mg/cm^2, depending on the amount of underlying PEG1500 layer, was selected to investigate the possibility of reducing the amount of polymer needed to act as an anti-sticking film.

Compaction force was explored at two levels, *i.e.* the minimum value that preliminarily yielded manageable units without damaging the pellet structure and two-fold this minimum value. Notably, the compaction force (about 1 kN) set as the minimum value with the newly adopted punches (oblong tablets) corresponded to the pressure (about 7 MPa) exerted to attain the cylindrical tableted MUPSs. For each factor, the edges of the interval were transformed to -1 and +1 in normalized scales and the central values were set to 0. The factor levels relevant to the applied DoE are listed in Table 5.

335

336 *Table 5. Levels of DoE factors*

Factor		Levels		
		-1	0	+1
A	Amount of cushion coating (WG_C)	30%	40%	50%
B	Amount of anti-sticking coating (WG_A)	5%	-	10%
C	Compaction force (F_a)	F_a min	-	$2F_a$ min

337

338 Responses selected to describe the properties of the tableted pellets included tensile strength (TS),
339 disintegration time (t_{dis}) and percentage of tracer released after 2 h in pH 1.2 buffer ($\%AAP_{2h}$).

340 Due to the number of factors and levels involved, a $3x2^2$ full factorial DoE was carried out, and the relevant
341 final matrix involving 12 trials to prepare tableted MUPSs is shown in Table 6. To accomplish this task, six
342 different batches of pellets were prepared, each one being split into equal parts and tableted at the two
343 selected force levels.

344

345 *Table 6. DoE matrix for the manufacturing of tableted MUPSs*

Batch trial	levels of factors		
	WG_C	WG_A	F_a
1	-1	-1	-1
2	-1	+1	-1
3	0	-1	-1
4	0	+1	-1
5	+1	-1	-1
6	+1	+1	-1
7	-1	-1	+1
8	-1	+1	+1
9	0	-1	+1
10	0	+1	+1
11	+1	-1	+1
12	+1	+1	+1

346

347 All the batches of pellets devised by the DoE matrix were successfully manufactured, resulting in units with
348 good technological characteristics. Satisfactory process yields, ranging from 86% to 93% for all the coating
349 steps, were obtained. Moreover, units coated with KIR both at 5 and 10% w.g. did not show any tendency to
350 aggregate or stick to the polythene bag. From all pellet formulations, it was possible to prepare tablets at the
351 two levels of F_a. The typical aspect of a tableted MUPS is displayed in Figure 7, where photographs and
352 photomicrographs of a sample from trial #6 are reported by way of example (50% w.g. and 10% w.g. of PEG

and KIR, respectively, and 1 kN compaction force). After tableting, the compacted pellets were still distinguished, and some of them appeared deformed without any noticeable sign of fragmentation. External subunits, which came into contact with the punches, show more pronounced morphological changes. This apparently resulted in exposure of the inner coatings. From Figure 7d, which shows the cross-section of a manually broken tablet, it can be noted that the units positioned internally also changed in shape, which could mainly be attributed to easy plastic deformation of the PEG1500 layer.

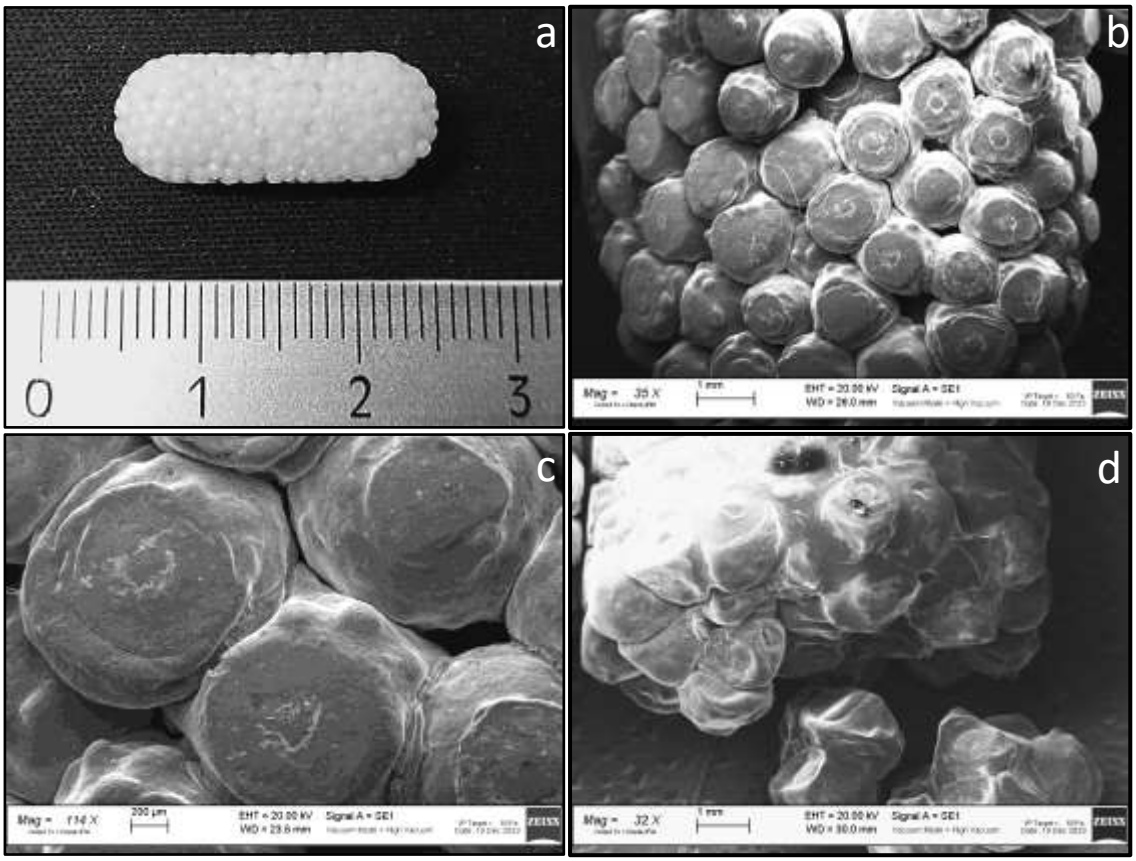

Figure 7. Tableted MUPS obtained from cushion-coated pellets (sample from trial #6 of DoE): digital photograph (a), SEM photomicrographs of the tablet surface at different magnification (b and c) and of a manually cross-sectioned tablet (d).

The results of characterization of MUPS tablets obtained from DoE trials are reported in Table 7 together with the actual values of the factors involved in their production.

Table 7. Values of factors and responses obtained in DoE trials

Batch trial	Factors			Responses		
	WG_C (%)	**WG_A (%)**	**F_a (kN)** mean ±sd	**TS (N/mm^2)** mean ±sd	**t_{dis} (min)** mean (CV<10)	**$\%AAP_{2h}$** mean (CV<10)
1	28.64	6.89	1.31 ±0.10	0.0561 ± 0.0062	9.75	0.0
2	28.64	11.43	1.27 ±0.08	0.0502 ± 0.0054	11.40	0.0
3	40.70	4.97	1.20 ±0.09	0.0842 ± 0.0077	11.10	0.0
4	40.70	9.61	1.18 ±0.11	0.0537 ± 0.0048	11.75	0.0
5	49.26	6.39	1.25 ±0.12	0.1039 ± 0.0091	12.43	0.0
6	49.26	12.80	1.20 ±0.04	0.0903 ± 0.0081	11.62	0.0
7	28.64	6.89	2.67 ±0.18	0.0823 ± 0.0076	25.43	0.6
8	28.64	11.43	2.75 ±0.31	0.1036 ± 0.0093	33.67	0.8
9	40.70	4.97	2.78 ±0.22	0.1456 ± 0.0133	20.92	1.0
10	40.70	9.61	2.68 ±0.28	0.1499 ± 0.0125	24.37	1.3
11	49.26	6.39	2.53 ±0.24	0.0980 ± 0.0096	20.01	1.9
12	49.26	12.80	2.60 ±0.27	0.1722 ± 0.0145	23.82	1.2

At a first analysis of the data collected, all the batches of tablets appear to fulfil gastro-resistance requirements, even though the ability of the MAE film to prevent release of the tracer in acidic environment would be affected, at least to some extent, by the compaction force.

All tableted MUPSs obtained at the lower resistance level (trials 1-6) disintegrated within 15 min, while with those manufactured at the higher level, disintegration time ranged between 20 and 35 min. Such disintegration times, if confirmed *in vivo*, would give rise to an early dispersion of the subunits in the stomach, and the process would in any case be sufficiently rapid to allow for a good biopharmaceutical performance of MUPS in terms of transit through the gastrointestinal tract.

Finally, as regards tensile strength, the mean values of batches obtained at the lower level of F_a was much lower than that of batches compacted at the higher F_a (0.0731 *vs.* 0.1253), although the trend of individual values in the two groups seems not to closely correlate with the relevant compaction forces.

The data collected were processed to calculate the coefficients of the mathematical model describing the relationship between each response and the factors considered in the study (Eq. 5)

$$y = b_0 + \Sigma b_i x_i + \Sigma b_{ij} x_i x_j + \Sigma b_{ii} x_i^2 \qquad (5)$$

where:

- y is the value of the response (dependent variable) under evaluation
- x_i and x_j are the levels of the i^{th} and j^{th} factors (independent variables) involved in the study ($A=WG_C$, $B=WG_A$, $C=F_a$)
- b_0 is the intercept
- b_i are the linear coefficients of i^{th} factor (where i indicates one of the 3 factors)

- b_{ij} are the coefficients of the interaction between i^{th} and j^{th} factors
- b_{ii} are quadratic coefficients of i^{th} factor

Calculation of the above-mentioned coefficients was performed by multiple linear stepwise regression using the least squares method to maximize R^2_{adj} value. Error probability values (p) were computed using Student's t-test. The regression and correlation coefficients obtained for the mathematical models of each response are shown in Table 8.

Table 8. Regression and correlation coefficients of mathematical models of each response

Polynomial Terms	Regression coefficients (p values in brackets)		
	TS	t_{dis}	$\%AAP_{2h}$
Intercept	0.0989* (0.000)	18.40* (0.000)	0.58* (0.000)
b_A	0.0240* (0.012)	-1.09* (0.011)	0.26* (0.013)
b_B		2.53* (0.001)	
b_C	0.0301* (0.002)	7.65* (0.000)	0.61* (0.000)
b_{AB}		-1.45* (0.016)	
b_{AC}		-2.61* (0.002)	0.25* (0.029)
b_{BC}		1.96* (0.002)	
R^2_{adj}	0.69	0.99	0.88

(A)WG_C (B) WG_A (C) F_a

* p values <0.05

Mathematical modelling of tensile strength (TS) led to a polynomial equation having low intercept value and positive coefficient for factors A and C, meaning that the obtained tableted MUPSs have poor mechanical resistance and this attribute could be improved by increasing the level of PEG1500 coating and of compaction force.

With regard to disintegration time, the relevant equation displayed an intercept value of approximately 18 min, a negative effect of A and positive effects of B and C. However, the importance of these contributions, as quantified by the values of their coefficients, was diverse. In particular, the levels of PEG and KIR coating brought about a relatively modest shortening and lengthening of the disintegration time, respectively, while compaction force, as previously observed, remarkably affected this response.

The relationship between disintegration time and each individual factor turned out linear, and significant interactions between them were found. The value of the correlation coefficient (R^2_{adj}) for this model pointed out its excellent ability to describe the results obtained.

Finally, maintenance of the functionality of the gastro-resistant coating after compaction of the units was also well described by the relevant mathematical model. In this case, the amount of PEG and compaction

force showed a positive though slight effect on the response, meaning that an increase in these factors would lead to an increase in $\%AAP_{2h}$, which, however, remains largely within the compendial limit.

To evaluate the reliability of the proposed system in the experimental space explored by the DoE, a desirability function simultaneously considering the three responses was set. This composite desirability function (D) was calculated as the geometric mean of the individual desirability functions of the responses (d_i) equally weighed to give same relevance to the different properties (Eq. 6).

$$D = \sqrt[3]{(d_A * d_B * d_C)} \qquad (6)$$

In more detail, the value of each response (y_j) was transformed into an individual desirability value (d_j), ranging between 0 and 1, according to the desired outcome, *i.e.* d_j =0 was assigned when the response was not acceptable and =1 when it was optimal (Table 9).

Table 9. Individual desirability functions and their intervals for each of the three responses studied by DoE

Response (y_j)	Level ranges of y_j	individual desirability functions (dj)
TS (N/mm^2)	$0 \le y_j < 0.1$ $y_j > 0.1$	$y_j/0.1$ 1
t_{dis} (min)	$0 \le y_j < 30$ $y_j > 30$	$(30-y_j)/30$ 0
$\%AAP_{2h}$	$0 \le y_j < 10$ $y_j > 10$	$(10-y_j)/10$ 0

In Figure 8, the trend of the composite desirability function is reported along with the optimal combination of values calculated for the three variables. The resulting desirability is high, with a maximum value of 0.832 and minimal changes throughout the experimental space explored for the pellet formulation. On the other hand, a greater impact was highlighted for compaction force. Overall, the analysis performed using DoE demonstrated the robustness of the approach proposed for developing tableted MUPS.

Figure 8: Trend of the composite desirability function and optimized conditions for manufacturing of tableted MUPS s

5. Conclusions

A new formulation strategy was proposed to convey modified-release pellets into tablets without the need for mixing with external cushioning excipients. Gastro-resistant film-coated pellets, provided with an outer layer of PEG1500, a soft and soluble material, led upon compaction to tablets with good mechanical properties even under relatively low forces, which allowed their original release performance to be

maintained after tablet disintegration. An additional film of Kollicoat® IR solved adhesion problems connected with the use of PEG1500, causing tablets to stick to each other and to their primary packaging. Despite the multilayer structure of the final MUPSs, the manufacturing of tableted pellets could be easier and more cost-efficient as compared with pellet-filled hard-gelatin capsules, also considering the important benefits offered to the patient.

CRediT authorship contribution statement

Saliha Moutaharrik: Methodology, Formal analysis, Investigation, Writing – original draft
Luca Palugan: Conceptualization, Formal analysis, Investigation, Writing – original draft
Matteo Cerea: Methodology, Formal analysis, Data curation.
Ilaria Filippin: Validation, Investigation, Visualization
Alessandra Maroni: Methodology, Writing – review & editing, Supervision.
Andrea Gazzaniga: Conceptualization, Methodology, Resources, Writing – review & editing, Supervision.
Anastasia Foppoli: Conceptualization, Methodology, Data curation, Writing – review & editing, Supervision, Project administration.

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