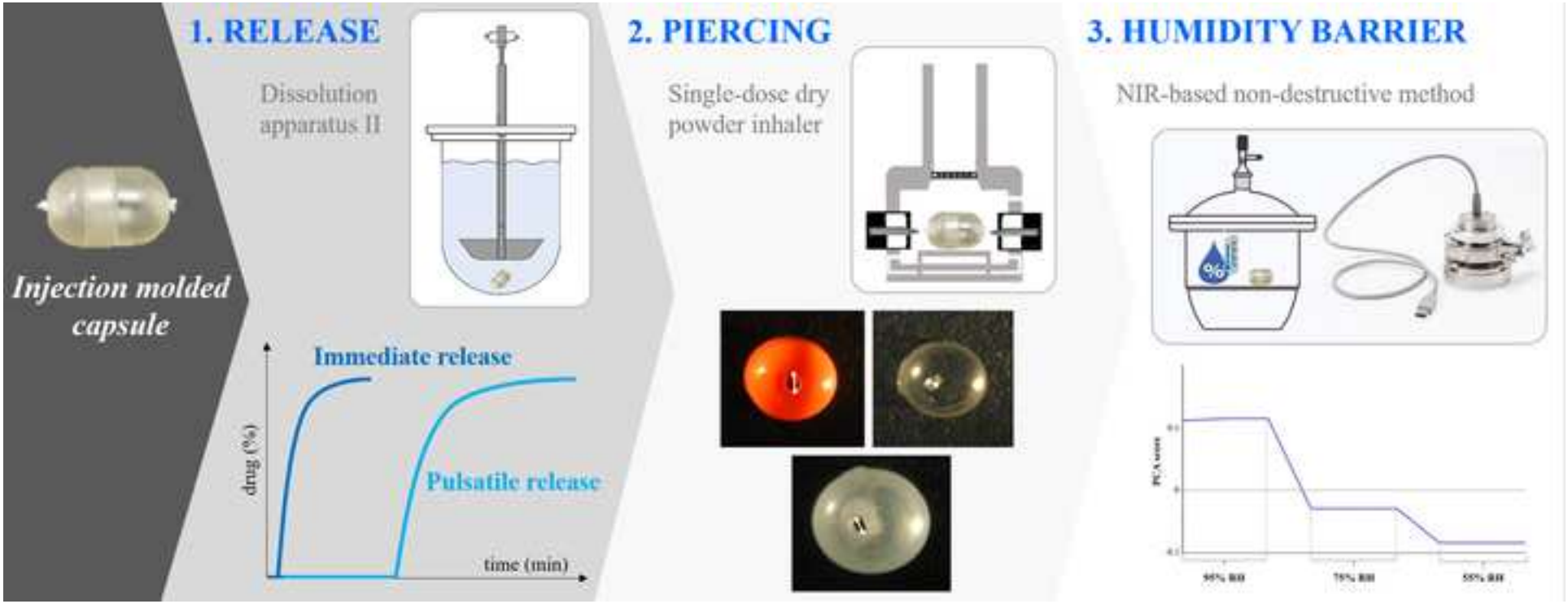
Graphical Abstract revised



Polyvinyl alcohol-based capsule shells manufactured by injection molding as ready-to-use moisture barriers for the development of delivery systems

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Abstract

In this work, feasibility of injection molding was demonstrated for manufacturing capsule shells. 600µm-thick prototypes were successfully molded with pharmaceutical grade low viscosity polyvinyl alcohols (PVAs), possibly added with a range of different fillers. They showed reproducible weight and thickness (CV < 2 and 5, respectively), compliant behavior upon piercing (holes diameter analogous to the reference), tunable release performance (immediate and pulsatile), and moisture protection capability. To assess the latter, an on-line method relying on near infrared spectroscopy measurements was set-up and validated. Based on the data collected and considering the versatility IM would provide for product shape/thickness/composition, PVA-based molded shells could help widening the portfolio of ready-to-use capsules, representing an interesting alternative to those commercially available. Indeed, these capsules could be filled with various formulations, even those with stability issues, and intended either for oral administration or for pulmonary delivery *via* single-dose dry powder inhalers.

1. Introduction

To date, materials and techniques borrowed from pharmaceutical-adjacent industrial sectors have contributed to innovations in drug delivery system (DDS) development [Uboldi et al., 2022]. This translational approach to innovation may reduce time and cost of production, ease process scale-up, and increase the likelihood of achieving a patentable final product. It follows that electrospinning, 3D printing, and 4D printing - currently used in biomedical, plastics and mechanical industry - have recently gained major traction in pharmaceutical manufacturing [Antezana et al., 2023; Inverardi et al., 2021; Lian et al., 2024; Luraghi et al., 2021; Mahmoud et al., 2023; Melocchi et al., 2020a,2021; Miliken et al., 2024; Muhindo et al., 2023; Ravasi et al., 2023; Uboldi et al., 2024]. Even before the advent of 3D printing, processing techniques employed for plastic transformation, such as hot melt extrusion (HME) and injection molding (IM), attracted considerable interest, mainly due to their suitability for large-scale and continuous manufacturing [Kallakunta et al., 2019; Patil et al. 2024; Sarabu et al., 2019]. In particular, IM was explored for the flexibility it would provide in creating achievable and well-defined shapes with micrometric details [Zema et al., 2012]. Besides advantageous technological characteristics, molded products exhibit interesting biopharmaceutical features towards either fast or prolonged release. While the former benefits from solid molecular dispersion of the drug into a polymeric carrier, the latter is favored by highly dense products resistant to the so-called burst effect. Recent interest in green and eco-friendly pharmaceutical processes has provided further motivation towards implementing IM, due to its avoidance of organic solvents and reduction of overall energy consumption [Ang et al., 2021; Becher et al., 2022; Milanesi et al., 2020]. For these reasons, IM has been proposed in the drug delivery field either as an alternative method for reducing the costs associated with existing products or as a suitable tool for manufacturing novel products with improved design and performance characteristics. Thus, alongside the extensive literature focused on the feasibility of IM in the manufacturing of prolonged-release DDSs, such as oral matrices, implants and inserts, the technique was also proposed to produce hollow structures [Clark et al., 2012; Clayes et al., 2012; Gazzaniga et al., 2011; Murphy et al., 2018; Verstraete et al.,

2016; Zema et al., 2012]. The resulting systems resembled already available hard capsules, but had different release performance, ensuring controlled release of the active ingredient conveyed. Indeed, the composition and design features (*e.g.* morphology, thickness) of the shell were responsible for the release of its content [Benzine et al., 2021; Casati et al., 2020; Zema et al., 2013a,b]. In addition, by combining molded shells with 3D printed internal partitions, multi-compartment capsules were obtained, thus increasing the associated customization opportunities [Melocchi et al., 2020b]. Varying the polymeric formulations assigned to each compartment facilitates complex release kinetics and filling of multiple, formerly incompatible active ingredients.

Among the materials already used to produce commercial capsules by dipping, gelatin could be processed at limited costs [Gullapalli et al., 2017]. However, it is incompatible with certain active ingredients/excipients and its animal origin poses major challenges when users have specific dietary and religious restrictions. In this respect, hydroxypropyl methylcellulose (HPMC) was deemed a promising alternative [Al-Tabakha 2010; Majee et al., 2017]. In fact, it is a vegan-compliant ingredient, processable by dipping and characterized by lower compatibility issues.

Although gelatin- and HPMC-based capsules are the blockbuster on the market, they still possess limited moisture protection [Chang et al., 1998; Missaghi et al., 2006; Yang et al., 2020]. Such a limitation may impair their broad use in oral drug products as well as food supplements and as carriers for powders intended for pulmonary administration *via* dry-powder inhalers (DPIs) [Buttini et al., 2021; Ding et al., 2021; Lavorini et al., 2017]. In this respect, major exchange of moisture with the outer environment, resulting in water vapor absorption, from the conveyed formulation, should be avoided.

Preliminary findings, reported both in the scientific literature and in technical reports focused on coating formulations already on the market, suggested the potential for poly(vinyl alcohol) (PVA) films to act as protective barriers against water vapor absorption [Channa et al., 2022; Liu et al., 2022; Oun et al., 2022; Yan et al., 2019]. As a result, this polymer is currently employed as film-coating agent to improve the stability of food supplements and active ingredients [Halake et al., 2014; Yang

et al., 2019]. Indeed, PVA is a thermoplastic synthetic polymer with water solubility, which makes it suitable for a wide range of industrial applications [Halima, 2016; Melocchi et al., 2019a,b; Wong et al., 1996]. By way of example, PVA was initially tested in additive manufacturing as a support material, and later as a primary component of 4D printed structures [Couti et al., 2024; Mallakpour et al., 2022; Uboldi et al., 2021, 2023]. Recently, PVA-based films fabricated by hot-processing have raised significant interest in the food packaging sector [Oun et al., 2022]. Besides providing transparency, thermal stability and mechanical properties comparable to the gold standard in the field made of low-density polyethylene, those based on PVA exhibit biodegradability and marked water/gas barrier properties, which could prolong the shelf-life of fresh foods. To enhance these favorable features while maintaining the environment-friendly nature of such films, PVA-blends containing a range of natural excipients (*e.g.* starch, chitosan, cellulose) were also studied [Panda et al., 2022; Russo et al., 2009; Zhang et al., 2024].

The aim of the present work was to demonstrate the potential of PVA-based molded capsules in novel DDSs that overcome the limitations currently associated with commercially available capsules. To broaden the application opportunities of such molded shells, which already take advantage of the geometric and dimensional versatility provided by the manufacturing technique, the resulting prototypes were evaluated for moisture protection, release, and piercing performance. Moreover, a non-destructive method based on on-line near infrared (NIR) spectroscopy was developed for the assessment of capsule water content.

2. Materials and Methods

2.1 Materials

Polyvinyl alcohol (PVA) of different molecular weight (commercial names: Gohsenol® EG 03P and EG 05P with a viscosity in the 3.0-3.8 and 4.5-6.1 mm^2/s range, respectively; sourced from Nippon Goshei, Japan; abbreviation: **PVA03** and **PVA05**); glycerol (sourced from Pharmagel, Italy; abbreviation: **GLY**); high amylose corn starch (commercial name: Amylo N-460, sourced from Roquette, France; abbreviation:

AMY); cross-linked sodium starch glycolate (commercial name: Explotab® CLV, sourced from JRS, Germany; abbreviation: **EXP**); talc (sourced from A.C.E.F., Italy); acetaminophen (sourced from Rhodia, Italy; abbreviation: **AAP**); Kollicoat IR® brilliant blue (sourced from BASF, Germany); gelatin and HPMC capsules size 3 and 0 (sourced from Capsugel, Italy).

2.2 Methods

2.2.1 IM of capsule shells

PVA03 and PVA05 underwent a milling step to reduce their particle size. This process was carried out using an ultra-centrifugal mill (ZM 200, Retsch, Germany), set at 14000 rpm and equipped with a 120 µm net. The feeding rate was manually controlled by slowly adding a pre-determined mass of material (≤ 10g) to reduce the chances of overheating and thus of PVA melting. PVA and all the other powder excipients used as fillers in this work were kept in an oven at controlled temperature (40 °C, 8 h, VWR, Italy) before use. Plasticized PVA formulations containing 15% by weight of GLY (calculated on the dry polymer) were prepared by kneading. Milled PVA powder was placed in a mortar and the liquid plasticizer was introduced dropwise under continuous mixing. Fillers were added to the plasticized PVAs by mixing in a mortar and their amount was expressed as % by weight with respect to the plasticized polymer. In more detail, formulations containing increasing percentage of fillers (up to 30%) were prepared. While talc was added as such, in the case of AMY- and EXP-containing formulations, even the fillers needed a plasticizer [Melocchi et al., 2015]. In this respect, GLY and distilled water were added to EXP and AMY before mixing with plasticized PVA. Therefore, the overall amount of these excipients in the final formulations not only included the selected starch derivatives but also their plasticizers. In Table 1, the composition of the formulations prepared and the relevant identification codes are summarized.

Table 1: composition (% by weight) and identification code of PVA-based formulations

x*		y*		
Polymer	**Plasticizer**	**Filler**	**Plasticizer**	**Formulation Code***
PVA03	15% GLY	/	/	PVA03
		AMY	15% GLY +12% H_20	$PVA03_{x\%}$ + $AMY_{y\%}$
		EXP	15% GLY +12% H_20	$PVA03_{x\%}$ + $EXP_{y\%}$
		TALC	/	$PVA03_{x\%}$ + $TALC_{y\%}$
PVA05	15% GLY	/	/	PVA05
		AMY	15% GLY +12% H_20	$PVA05_{x\%}$ + $AMY_{y\%}$
		EXP	15% GLY +12% H_20	$PVA05_{x\%}$ + $EXP_{y\%}$
		TALC	/	$PVA05_{x\%}$ + $TALC_{y\%}$

*x and y indicat the two main components of the formulation (*i.e.* plasticized PVA and the excipients added, eventually plasticized), whose percentage ranged between 70%-95% and 5%-30%, respectively.

The IM process was performed using a bench-top micromolding machine (BabyPlast 6/10P, Cronoplast S.L., Rambaldi S.r.l., Italy), provided with a single-cavity mold [Zema et al., 2013a]. The latter included two interchangeable inserts for the manufacturing bodies or caps with a constant nominal thickness of 600 µm. Moreover, such a mold was characterized by *i)* a hot runner, to maintain the desired temperature during cavity filling, *ii)* a 1.5 length/diameter ratio to limit the flow path, *iii)* a centered injection position to balance the flow of the material in all directions, *iv)* a halved thickness in the open contact areas between bodies and caps to ensure a constant thickness of the capsular device once assembled and *v)* an inner duct for injection of compressed air to ease part ejection. Thanks to the action of a loading piston, polymeric formulations were first loaded from a hopper into the micromolding equipment, specifically its plasticating chamber. The chamber worked as a reservoir containing heated spheres to promote mixing of the polymeric formulation. A certain amount of material (charge, C), defined by the final position of a second dedicated injecting plunger (ø = 10 mm), was then pushed from the plasticating chamber into the mold cavity through the 1 mm nozzle. This plunger acted in pressure control and was responsible for both injection and holding phases. Indeed, it applied the injection pressure (P_1) and the subsequent packing pressure (P_2),

maintained for 2.5 and 1.5 s, respectively. Constant P_1 and P_2 values were maintained by moving the injection piston at pre-selected rates (r_1 and r_2 for injection and holding, respectively), which were expressed as a percentage of the maximum rate. Four different temperatures (T_1-T_4) were set throughout the equipment, where T_4 was that relevant to the hot runner system. The experimental protocol applied to identify appropriate operating conditions is described in the Results and Discussion Section.

2.2.2 Characterization of capsule shells

Physico-technological characteristics: capsule bodies and caps were checked for weight (analytical balance BP211, Sartorius, D; n = 10) and thickness (MiniTest FH7200 equipped with FH4 probe, ø sphere = 1.5 mm, ElektroPhysik, D; n = 10). Digital photographs (Nikon D70, Nikon, J) were also taken (Figure 1).

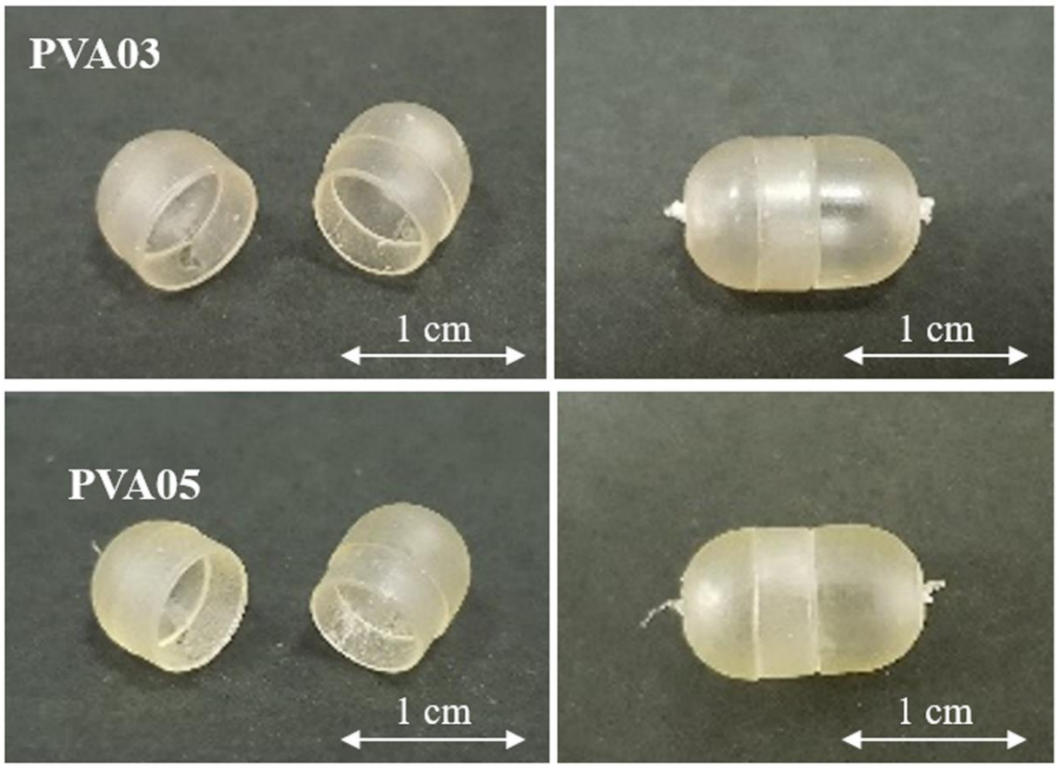


Figure 1: photographs of bodies and caps, as such or upon assembly, based on plasticized PVA03 and PVA05.

Opening in aqueous fluids: capsule bodies, manually filled with 50 mg (coefficient of variation, CV ≤ 2) of Kollicoat IR® brilliant blue were closed with matching caps. The filled/assembled capsules were glued on a microscope slide and immersed in unstirred distilled water at room temperature. This was done to avoid floating of the capsules into the medium, to maintain them in a fixed position to better observe their behavior upon contact with fluid. Digital photographs were taken at successive time points (GoPro Hero Session, US-CA).

Drug release: capsule bodies (n = 6), manually filled with 80 mg (CV ≤ 2) of AAP, were closed with the matching caps and inserted into sinkers, as suggested by the European Pharmacopeia. The shells prepared this way were then tested according to two different methods, either in *i)* a dissolution apparatus (USP 38 apparatus 2, Dissolution System 2100B, Distek, NJ-US; 800 mL distilled water kept at 37 ± 0.5 °C, paddle 100 rpm) or in *ii)* a 3 position disintegration apparatus (Sotax, CH), with each basket-rack assembly moving at 31 cycles/min in a separate vessel (800 mL distilled water kept at 37 ± 0.5 °C; one sample inserted in each basket-rack). In both cases, fluid samples were automatically withdrawn every 5 min by a peristaltic pump (Ismatec, I). The latter was connected to a UV spectrophotometer (Lambda 35, Perkin Elmer, I) to assess the amount of drug released over time (1 mm optical path cuvette, $\lambda = 245$ nm) taking advantage of a purposely built calibration curve ($y = 64.3072x$, $R^2 = 1.000$). By linear interpolation of release data immediately before and after the time point of interest, time to 10%, 80% and 90% release ($t_{10\%}$, $t_{80\%}$ and $t_{90\%}$ respectively) were calculated.

Piercing: PVA-, gelatin- and HPMC-based bodies and caps, maintained in a fixed position thanks to a plastic holder, were manually pierced in their rounded area with a pin removed from a DPI (DPI RS01®, Plastiape, I). To evaluate the possible influence of piercing force variability, size 3 gelatin and HPMC closed capsules, which were dimensionally compatible with the DPI RS01®, were also pierced using the assembled DPI. The pierced samples were photographed and the images were processed with a specific software (ImageJ, US-MD) to determine the diameter of the resulting hole.

When the hole did not appear symmetrical, the major diameter was measured. Photographs of manually pierced bodies and caps are reported in Figure 2.

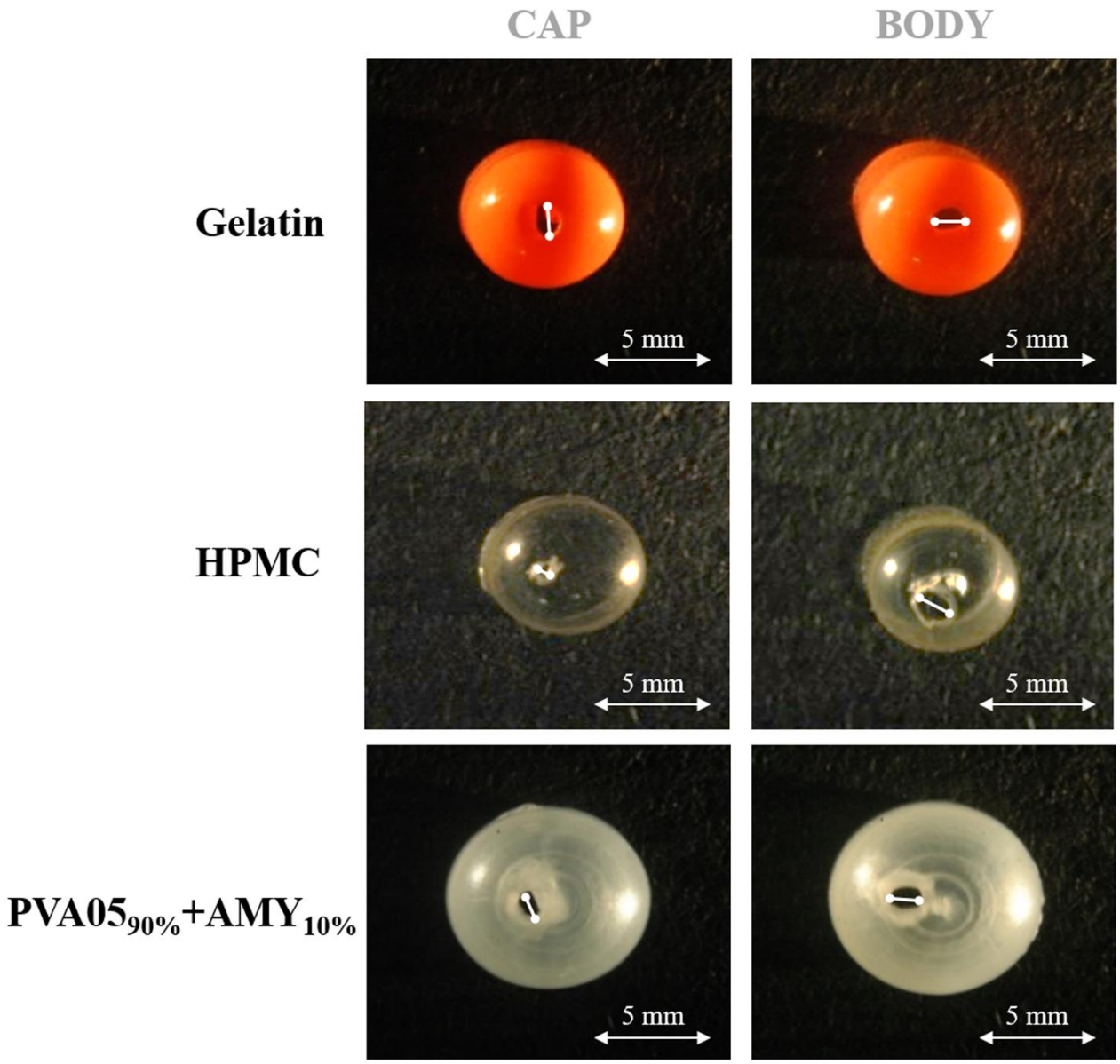


Figure 2: photographs of pierced bodies and caps having different composition, highlighting the diameter of the resulting hole.

Moisture content: AAP powder, empty shells and capsules filled with approximately 80 mg of AAP (CV ≤ 2%) were placed into desiccators containing different saturated salt solutions. These were stored in an oven set at 40 °C (VWR, I) to create environments with pre-defined humidity (*i.e.* $MgNO_3$

saturated solution for 48.42 ± 0.37 RH%, NaCl saturated solution for 74.68 ± 0.13 RH% and K_2SO_4 saturated solution for 96.41 ± 0.38 RH%). RH was monitored with a calibrated hygrometer. Samples were withdrawn at different time points to assess the water content, determined by:

- loss on drying (LOD) experiments (110 °C for 30 min) making use of a thermobalance (VWR, I);
- Karl Fisher titration (Mettler DL50 Graphix equipment, Mettler Toledo GmbH, CH), in the case of AAP powder. The tracer powder was dissolved in anhydrous methanol and the resulting solution was titrated with Hydranal® Composit 5 (Fluka Analytical, US-MA);
- near infrared (NIR) diffuse reflectance spectrometry (VIAVI Solutions MicroNIR PAT-U, I).

For the latter method, a calibration curve correlated the measured parameter (*i.e.* the water content) and the spectra collected by the NIR probe. For different capsule shells and AAP powder removed from the same desiccator, where they were maintained under specific humidity conditions, samples (n = 3) were checked for moisture content via either LOD tests or Karl Fisher tritation. In parallel NIR spectra were also acquired (mean of 500 counts acquired every 10 s). The sensor focus was about 1 cm from the probe tip and it was pointed at the center of the specimens. As avoiding changes in the focus point from sample to sample was fundamental, a special support with a threaded flange was screwed on the head of the NIR probe, which was mounted on welded pins to keep it in a constant position. The measurements collected were analyzed and processed using the CAMO Unscrambler® software. Since non-chemical effects, such as product temperature, relevant movement and slight differences in the positioning of the probe, would affect the baseline of the spectra acquired, both Standard Normal Variate (SNV) and first derivative were enforced. More into detail, the SNV was applied to center and scale each individual spectrum, thus representing a sample-oriented standardization. Indeed, it allowed to eliminate both multiplicative interferences associated with scattering phenomena as well as particle size effects, and to center, on the vertical scale, each spectrum on the zero value. Then, the first derivative of the spectra was calculated to resolve overlapped bands. This helped understanding the results, emphasizing small spectral variations that

cannot result evident from the raw data. The Principal Component Analysis (PCA) was performed as the last, to reveal hidden structures within relatively large data sets.

The spectra resulting from SNV, first derivative and PCA techniques were correlated to LOD data using the Partial Least Squares (PLS) regression method:

- $y = 0.9947x + 0.0470$, $R^2 = 0.995$ for AAP;
- $y = 0.9682x + 0.5638$, $R^2 = 0.968$ for PVA03-based molded capsules;
- $y = 0.9836x + 1.1484$, $R^2 = 0.984$ for PVA05-based molded capsules.

A predictability test was also performed. Starting from the original dataset, the software applied the so-called leave one out method and tried to hypothesize a calibration curve randomly eliminating one point at a time and forecasting a new distribution based on the remaining data. R^2 values of these curves turned out always above 0.950, leading to assess the robustness of the method developed.

3. Results

3.1 Injection molding

During this work, a screening mold was used for the alternate manufacturing of bodies and caps, which were then assembled in 600 µm-thick capsules. Two different PVA grades available on the market were selected, with increasing molecular weight and already approved by USP, EP as well as JP (*i.e.* PVA03 and PVA05). Commercially available size 0 gelatin and HMPC capsules were taken as a reference, due to their overall dimensional and volumetric comparability.

To enhance IM processability and improve the overall performance of the resulting shells, a preliminary formulation study was carried out, screening various plasticizers and fillers. While molding neat PVAs was challenging (the cycle was often interrupted to manually remove items from the mold due to their glassy nature), the presence of plasticizer proved essential for a continuous process resulting in complete parts that could be easily handled, filled and assembled.

A few excipients, such as talc, a high amylose starch derivative (AMY) and a cross-linked sodium starch glycol (EXP), were then added to the plasticized formulations replacing up to 30% of PVA. AMY and EXP were selected based on preliminary findings from food packaging literature, discussing the potential of blending PVA with starch-related materials *via* HME [Abedi-Firoozjah et al., 2023; Panda et al., 2022]. Indeed, under appropriate conditions (*i.e.* enough thermal and mechanical stress to achieve thermoplastic starch), films with improved mechanical and moisture barrier properties were obtained. Considering previous experiences with hot-processing starch derivatives in the lab, GLY and water mixtures were employed to plasticize AMY and EXP before adding them to the PVA-based formulation [Melocchi et al., 2015].

A working protocol was developed to objectively check IM processability, ensuring generation of an ample quantity of bodies and caps for subsequent characterization. The protocol envisaged a set of operations repeated in a specific sequence, introducing progressive modifications in heating and injection, while keeping constant the cooling conditions (*i.e.* 20 °C for 5 s). The temperature was the first parameter investigated, as temperature increase theoretically reduces the PVA melt-viscosity and favors mold filling. A gradual temperature increase was implemented to prevent equipment blockage and limit degradation phenomena. The starting temperature of the plasticating chamber (T_2) was selected based on preliminary DSC and HME data, while compression chamber (T_1) and nozzle (T_3) temperatures were set 5 °C below and above T_2, respectively. Finally, the hot runner (T_4) needed to heat to 15 °C above T_2, due to the limited amount of time the material would remain at this state. Regarding the injection conditions, two independent pressures (P_1 and P_2), each exerted for a pre-defined time (t_1 and t_2) and rate (v_1 and v_2), were set together with the quantity of injected material (C). While P_1 ensured filling of almost the entire volume of the mold cavity, P_2 stabilized the injected material and compensated for shrinkage. Conversely, the C parameter was defined volumetrically and calculated based on injecting piston displacement. For this reason, it was measured in mm. Finally, v_1 and v_2 maintained a uniform material temperature during the injection step. Indeed, if the injection speed was too low, the formulation cooled down before reaching all areas of the mold cavity.

Consequently, the injection piston's second movement to add a new shot of material would be impeded, resulting in an incomplete part. Low pressure values were initially implemented (*i.e.* 30 bar for P_1 exerted for of 0.8 s at 30% rate and 10 bar for P_2 applied for 0.3 s at 10% rate), to assess the resulting parts for completeness and for presence of visible imperfections. In the case of incomplete items, P_1, P_2 and rates were increased by 10 bar and 10%, respectively. Conversely, if the molded part was almost complete or had only small imperfections, only P_2 was increased by 5 bar. Whenever this change was insufficient, v_1 and v_2 were raised by 5% at a time and, lastly, t_1 and t_2 by 0.1 s. For all preliminary trials, a C value in the range of 4-5 mm was deemed suitable for ensuring complete filling of the mold cavity corresponding to the body of the capsular devices. This part was the biggest, requiring the most injected material. The same value was set for cap manufacturing.

Final operating parameters enabling the successful manufacturing of automatically ejected parts with all the formulations tested are reported in Table 2. The conditions relevant to filler-containing formulations are indicated as ranges because the values slightly differed depending on the amount of PVA replaced. The presence of fillers was demonstrated to modify the processability of the formulations, generally slowing or making the injection process harder, probably due to an increased viscosity of the melt. Consequently, process parameters and especially temperatures needed to be adjusted.

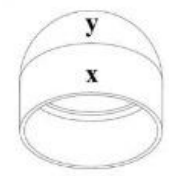
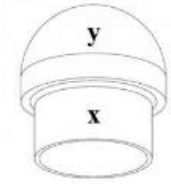
Table 2: IM operating condition set for the manufacturing of bodies and caps having different composition

Formulation Code*	**T_1 (°C)**	**T_2 (°C)**	**T_3 (°C)**	**C (mm)**	**P_1 (bar)**	**t_1 (s)**	**v_1 (%)**	**P_2 (bar)**	**t_2 (s)**	**v_2 (%)**
PVA 03	150	160	165	4	45	0.8	45	55	0.3	25
$PVA03_{x\%}$ + $AMY_{y\%}$	150-170	150-180	160-190	4	30-60	0.8-1.5	30-70	10-70	0.3-1.0	10-50
$PVA03_{x\%}$ + $EXP_{y\%}$	150-160	160-170	170-175	4	30-60	0.8	30-60	50-80	0.3	20-50
$PVA03_{x\%}$ + $TALC_{y\%}$	145-160	155-170	165-175	5	30-75	0.8-2.0	30-60	20-60	0.3-1.5	10-40
PVA 05	155	165	170	4	45	1.2	50	40	0.3	25
$PVA05_{x\%}$ + $AMY_{y\%}$	145-170	150-180	170-190	4	30-60	0.8-1.5	30-70	10-70	0.3-1.0	10-50
$PVA05_{x\%}$ + $EXP_{y\%}$	145-160	155-170	160-175	4	30-60	0.8	30-60	50-80	0.3	20-50
$PVA05_{x\%}$ + $TALC_{y\%}$	150-160	160-170	165-175	5	30-75	0.8-2.0	30-60	20-60	0.3-1.5	10-40

*x and y ranged between 70%-95% and 5%-30%, respectively.

The manufactured caps and bodies were checked for weight and thickness. Data relevant to PVA-based capsules with increasing filler amounts from none to high are reported in Table 3. In detail, shell thickness was measured both in the cylindrical open (x) and in the rounded closed (y) ends of bodies and caps, where expected values were 300 and 600 µm, respectively.

Table 3: weight and thickness data relevant to bodies and caps having different composition

	Weight, mg (CV)		**Thickness, µm (CV)**			
			Cap		**Body**	
	Cap	**Body**				
			x	**y**	**x**	**y**
PVA 03	126.74 (0.72)	138.54 (0.57)	338.80 (0.90)	843.32 (2.82)	352.58 (2.87)	595.45 (3.39)
PVA03$_{70\%}$ + AMY$_{30\%}$	126.71 (1.37)	136.75 (1.27)	333.35 (1.68)	836.10 (1.02)	343.57 (4.88)	593.97 (2.90)
PVA03$_{70\%}$ + EXP$_{30\%}$	140.28 (0.26)	128.65 (0.51)	352.27 (4.45)	845.05 (2.72)	345.22 (1.85)	591.43 (1.04)
PVA03$_{70\%}$ + TALC$_{30\%}$	141.78 (1.87)	153.20 (1.29)	347.40 (4.74)	854.12 (3.69)	362.70 (2.41)	616.83 (2.35)
PVA 05	126.55 (0.58)	138.70 (0.28)	355.38 (4.54)	855.10 (3.73)	348.12 (2.98)	614.80 (3.38)
PVA05$_{70\%}$ + AMY$_{30\%}$	120.78 (1.21)	132.91 (0.94)	346.32 (3.12)	847.67 (0.94)	347.48 (4.20)	603.43 (1.42)
PVA05$_{70\%}$ + EXP$_{30\%}$	127.23 (0.29)	138.95 (0.50)	345.75 (4.17)	817.22 (2.70)	350.88 (1.54)	601.77 (1.70)
PVA05$_{70\%}$ + TALC$_{30\%}$	142.04 (0.29)	155.11 (0.17)	357.18 (3.52)	860.38 (5.10)	351.58 (2.93)	610.30 (3.23)

Overall, the weight of the individual parts was reproducible independent of the molded formulation (CV < 2). The same consideration could be also drawn for thickness data: the resulting CVs were generally below 3 and always below 5. The cylindrical hollow area of bodies and caps, besides being the thinnest zone and thus the most challenging to obtain, was also responsible for pairing and locking. Its actual thickness illustrated a slight tendency of the PVA-based formulations towards expansion.

However, this did not impair the capsule assembly and closure. The larger thickness deviation in the rounded closed end of caps from the nominal 600 µm value was attributed to: *i)* different cooling rates in the various areas of the mold and *ii)* the presence of residual stresses in the injected material [Zema et al., 2012]. However, these aspects could be improved through the development of a dedicated mold, which will be conceived and built around the thermal characteristics of the formulation to be processed.

3.2 Properties and performance

3.2.1 Release

Molded prototypes filled with a dye powder were preliminarily immersed in unstirred water at room temperature, to verify the continuity of the shell walls together with the tightness of the closure. For all the capsules, independent of relevant composition, no major changes in structure were observed up to about 1 h of contact with aqueous fluids, and no dye leakage was detected in the sealing area. Such integrity was maintained during hydration and erosion/dissolution of the walls, until the occurrence of first rupture. After that, a prompt release of the dye was evident, with the surrounding media assuming a bluish color. This opening time was different depending on the specific formulation and was generally lower for PVA03-based capsules. For samples using the same PVA grade, the presence of fillers reduced opening time. Photographs of either PVA05 and $PVA05_{70\%}$ + $AMY_{30\%}$ capsular devices immersed in aqueous media are reported in Figure 3.

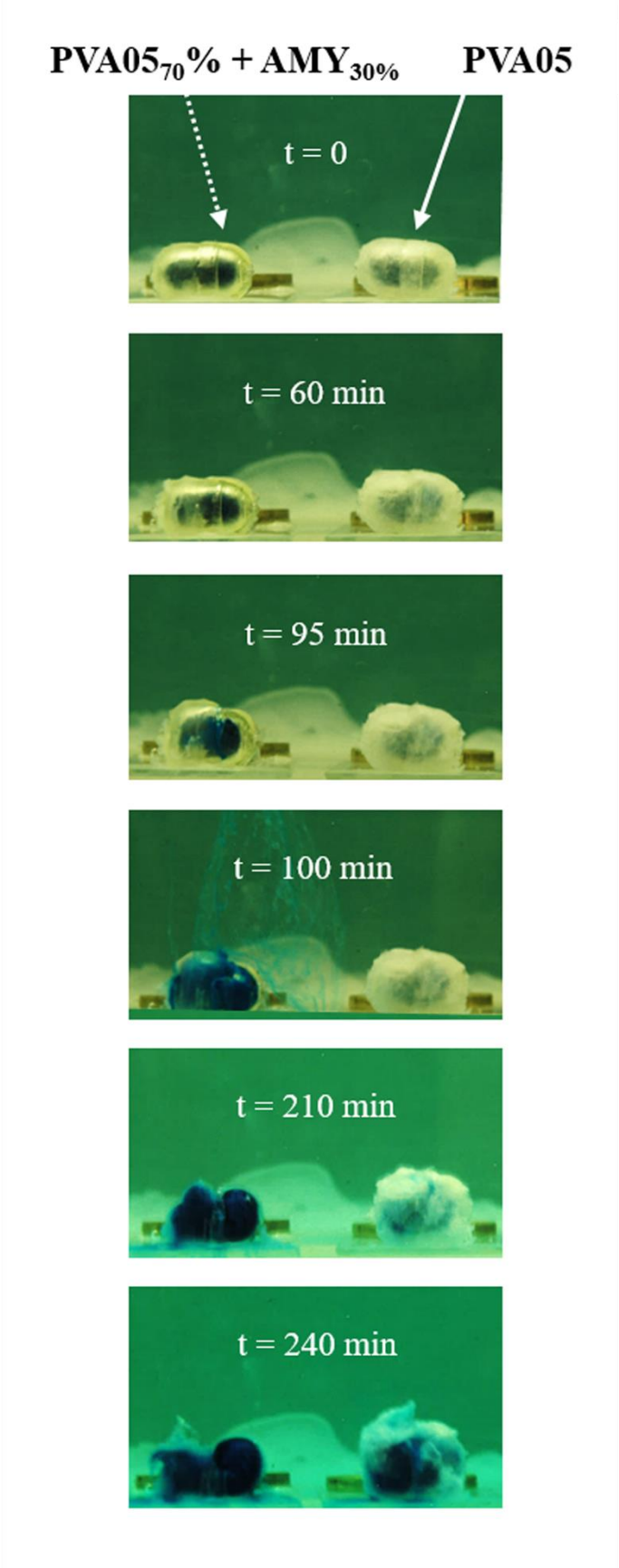


Figure 3: photographs of capsules having different composition taken at successive time points during the opening test.

Devices filled with AAP as a drug tracer were also tested for release. Both gelatin and HPMC capsules were evaluated for comparison purposes. Based on the swellable aptitude of PVA following hydration, molded shells were expected to undergo a glass transition with the formation of a gel layer, the rate of erosion/dissolution of which would depend on polymer molecular weight and composition/thickness of the capsule walls. Moreover, the presence of a gelled surface could affect the dissolution test due to a certain tendency of the capsules to stick to the vessel walls. The resulting adhesion, combined with possible detachment from the vessel, could either slow down the capsule opening, limiting its exposure to aqueous fluids, or force its early rupture with release of the content. In this respect, preliminary experiments already presented in the literature and comparing the release behavior of capsular devices tested under *i)* standard USP settings involving a dissolution apparatus II and *ii)* alternative ones, entailing for instance a purposely-assembled disintegration equipment, were useful to confirm this hypothesis and to identify the appropriate experimental setup [Gazzaniga et al., 1995, 2011; Zema et al., 2013a;]. For example, release profiles relevant to plasticized PVA03 and PVA05 capsules tested according to the two different conditions above described are reported in Figure 4. Although the average opening times were analogous, data reproducibility was higher for capsules tested in the disintegration apparatus. Therefore, the release method involving the use of this equipment was selected to further compare the capsules under development. To this end, a few release parameters were calculated (Table 4): *i)* the opening time of capsular devices ($t_{10\%}$), *ii)* the time to 80% release ($t_{80\%}$) and *iii)* that required to complete the release once it started ($t_{90-10\%}$).

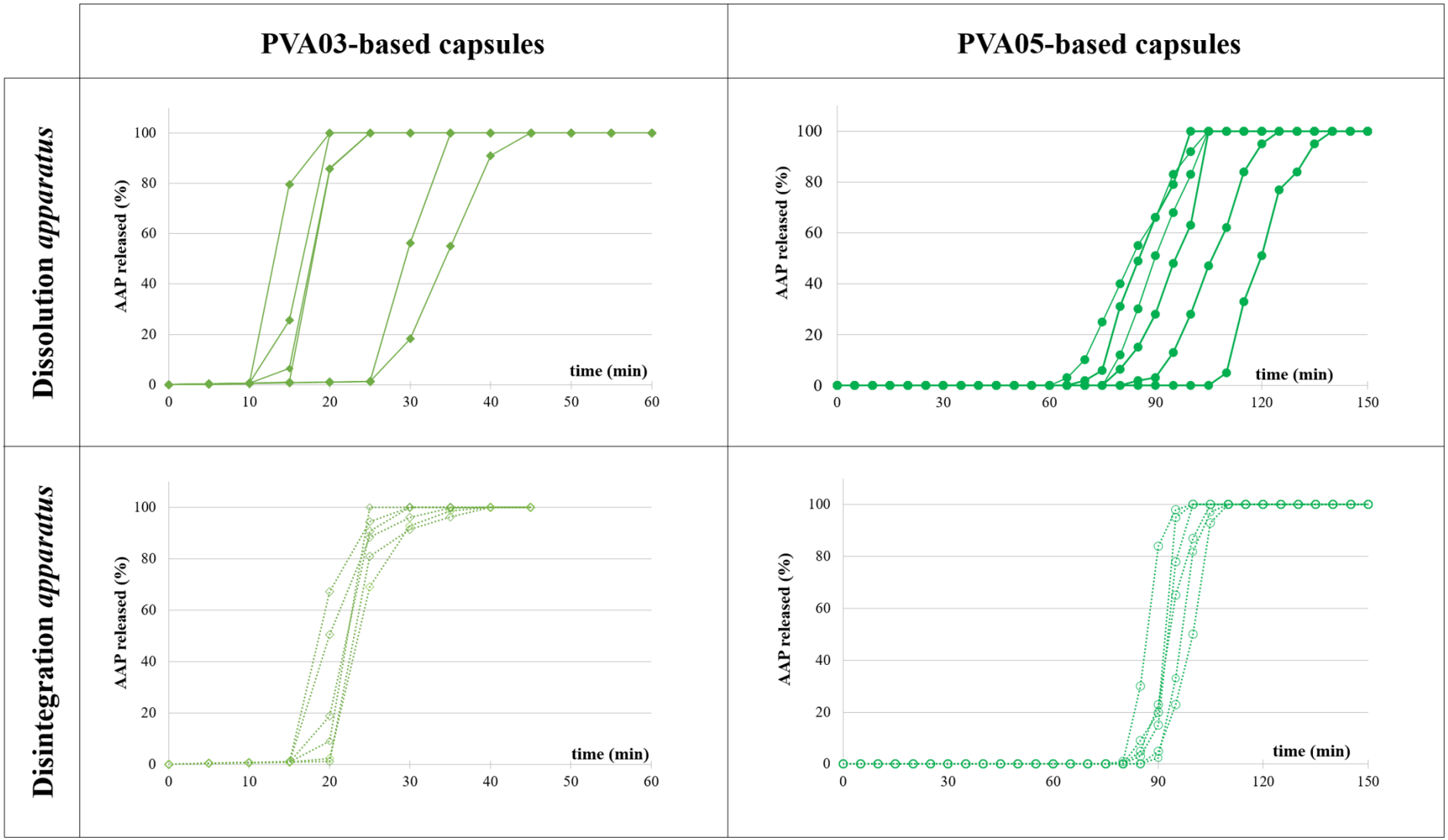


Figure 4: release profiles relevant to PVA03- and PVA05-based capsules tested in either in the dissolution or in the disintegration apparatus.

All systems displayed a lag phase preceding the loss of capsule integrity, followed by the release of the drug. In this respect, the $t_{10\%}$ would primarily depend on the hydration/erosion/dissolution behavior of the capsule walls and thus on composition and thickness. Interestingly, $t_{80\%}$ was shorter for gelatin and HPMC capsules (< 10 min), which are characterized by thinner walls, and 4 folds longer for PVA05 *versus* PVA03-based systems, due to the increased molecular weight of the main polymeric component. Moreover, when dealing with thicker capsules, the time until complete release tended to increase and seemed to be affected by the hydrodynamic conditions of the test, leading to a release performance similar to that of pulsatile-release systems. At the same time, the possibility of fine-tuning the lag time pointed out by 600 µm thick molded capsules based on the nature of the filler was demonstrated. In particular, adding EXP, AMY and talc in the plasticized PVA-based formulations proved a suitable strategy to reduce $t_{10\%}$ values. Although shorter lag times were achieved by just adding the lowest filler percentage, variability in the performance of such capsules was ruled out. To this end, increasing the load to 30% was particularly advantageous. This finding suggested the presence of a threshold amount for fillers, over which a reproducible decrease in the opening time could be obtained, probably thanks to a faster erosion/dissolution of the resulting PVA gel. A different behavior was observed when dealing with items molded from mixtures containing talc. The latter was expected to reduce PVA wettability and, by remaining suspended into the molten material, to promote the formation of a non-continuous gelled structure with faster erosion/dissolution. The above-mentioned phenomenon would explain the performance of PVA05 talc-containing capsules, for which a reduction in all the release parameters was obtained. However, when talc was added to plasticized PVA03, a worsening of device performance was highlighted (*e.g.* poor reproducibility and increase in capsule opening time), probably due to the reduced and more erratic polymer hydration rate.

EXP-containing PVA05 capsules exhibited a longer $t_{90\%-10\%}$, with a diffusive release of the drug tracer. This was attributed to the tendency of the devices to open following a clear separation of the swollen body from the swollen cap, with subsequent collapse and partial re-closing of the body containing the

tracer onto itself. Due to this unexpected phenomenon, the AAP release might depend on its capability to permeate the gelled layer of the capsule walls (at least until complete erosion/dissolution of the latter).

Table 4: release parameters relevant to capsules of different composition tested in the disintegration apparatus.

	$t_{10\%}$, min average ± std. dev.	**$t_{80\%}$, min** average ± std. dev.	**$t_{90\%-10\%}$, min** average ± std. dev.
Gelatin	2.58 ± 1.66	6.50 ± 1.86	2.52 ± 0.04
HPMC	5.4 ± 1.59	8.46 ± 0.49	2.96 ± 0.62
PVA03	18.38 ± 2.30	24.45 ± 1.64	6.68 ± 1.88
$PVA03_{90\%}$+$AMY_{10\%}$	14.66 ± 2.28	18.97 ± 1.96	5.23 ± 2.11
$PVA03_{70\%}$+$AMY_{30\%}$	9.20 ± 0.05	11.83 ± 0.36	3.61 ± 1.16
$PVA03_{90\%}$+$EXP_{10\%}$	17.64 ± 3.07	22.33 ± 4.23	4.66 ± 1.98
$PVA03_{70\%}$+$EXP_{30\%}$	15.03 ± 2.66	18.71 ± 2.62	5.18 ± 1.51
$PVA03_{90\%}$+$TALC_{10\%}$	34.12 ± 9.54	45.78 ± 8.37	36. 42 ± 6.84
$PVA03_{70\%}$+$TALC_{30\%}$	24.27 ± 8.07	33.48 ± 6.97	35.10 ±7.00
PVA05	87.97 ± 3.68	96.80 ± 4.84	10.87 ± 3.26
$PVA05_{90\%}$+$AMY_{10\%}$	29.06 ± 2.51	38.92 ± 5.20	9.71 ± 3.73
$PVA05_{70\%}$+$AMY_{30\%}$	18.12 ± 1.14	25.01 ± 0.92	9.47 ± 3.29
$PVA05_{90\%}$+$EXP_{10\%}$	31.24 ± 2.98	45.87 ± 3.01	12.44 ± 3.65
$PVA05_{70\%}$+$EXP_{30\%}$	22.89 ± 1.54	38.46 ± 5.37	19.60 ± 3.40
$PVA05_{90\%}$+$TALC_{10\%}$	43.13 ± 2.30	51.11 ± 3.87	9.87 ± 4.13
$PVA05_{70\%}$+$TALC_{30\%}$	24.48 ± 0.71	32.80 ± 2.18	10.66 ± 2.22

The PVA shell formulations containing 30% of AMY were the most promising, demonstrating an alternative to gelatin- and HPMC-based capsules. Indeed, the resulting capsules achieved $t_{80\%}$ values and pulse times analogous to those of commercial references, despite the presence of thicker walls

common for molded products. Moreover, for increasing the portfolio of capsules already on the market, IM was confirmed an interesting technique for manufacturing DDSs with tunable performance.

3.2.2 Piercing

In the so-called unit-dose DPI, an individual dose of the active ingredient to be administered is conveyed, in a powder form, within a commercially available capsule [Buttini et al., 2021; Hickey, 2023; Islam et al., 2008; Newman et al., 2022; Van Renswouw et al., 2010; Xiroudaki et al., 2021]. The drug is then released thanks to the patient's inspiratory flow, after the device ensured either the separation of the cap from the body or the creation of one or multiple holes into the capsule, using purposely positioned pins. Besides compatibility with large dosages, thus broadening the range of active molecules that could be inhaled, such DPIs are considered environment-friendly because they do not require the use of any propellant. Therefore, molded PVA-based shells could be an interesting alternative to traditional HPMC and gelatin capsules currently in use, first for the geometric versatility provided by IM. In fact, novel DPIs could be designed without having to adapt the device to the capsules already on the market since *ad hoc* ones, considering shape, dimensions and composition, could be purposely molded. In addition, IM ensures major weight reproducibility and, being performed at high temperature and pressure conditions, even low microbiological charge. Among all, one of the most peculiar features relevant to suitability of molded shells as DPI carriers is their piercing performance [Birchall et al., 2008]. The latter is intended as the possibility to create holes in the capsule walls that would not re-close after pin removal and would not generate potentially hazardous fragments. For this reason, capsule based on water soluble materials are especially promising. Indeed, undesired inhalation of soluble fragments might be less risky: gradual dissolution over time will not obstruct the airways and be recognized by the immune systems as dangerous foreign bodies. This is the main reason why, low polyethylene-based capsules, presented in many patents as carriers for DPIs because of their high moisture protection, never reached the market.

The behavior upon piercing of molded shells was preliminarily evaluated using gelatin and HPMC-capsules as a reference. In this respect, commercially available capsules were tested both upon insertion into a DPI and by piercing them with one of the pins removed from the same device. No major differences were noticeable between the two methods, thus proving the suitability of the manual one for evaluating bodies and caps manufactured by IM. The hole diameters are reported in Table 5. Besides gelatin and HPMC capsules, molded ones based on different PVAs and containing either 10 or 30% of fillers were tested.

Table 5: diameter of the holes attained by manually piercing capsules of different composition.

	Hole diameter, mm average ± std. dev.	
	Cap	Body
Gelatin	0.85 ± 0.23	1.29 ± 0.27
HPMC	1.30 ± 0.22	0.92 ± 0.29
PVA03	1.23 ± 0.36	1.47 ± 0.25
PVA03$_{90\%}$+AMY$_{10\%}$	0.99 ± 0.18	1.50 ± 0.24
PVA03$_{70\%}$+AMY$_{30\%}$	1.40 ± 0.32	1.33 ± 0.28
PVA03$_{90\%}$+EXP$_{10\%}$	1.27 ± 0.33	1.42 ± 0.31
PVA03$_{70\%}$+EXP$_{30\%}$	1.08 ± 0.15	0.97 ± 0.29
PVA03$_{90\%}$+TALC$_{10\%}$	0.86 ± 0.25	1.07 ± 0.25
PVA03$_{70\%}$+TALC$_{30\%}$	1.40 ± 0.30	1.39 ± 0.32
PVA05	1.35 ± 0.22	1.28 ± 0.28
PVA05$_{90\%}$+AMY$_{10\%}$	1.44 ± 0.19	1.11 ± 0.33
PVA05$_{70\%}$+AMY$_{30\%}$	0.88 ± 0.14	1.05 ± 0.22
PVA05$_{90\%}$+EXP$_{10\%}$	1.41 ± 0.3	1.38 ± 0.27
PVA05$_{70\%}$+EXP$_{30\%}$	1.26 ± 0.18	1.49 ± 0.38
PVA05$_{90\%}$+TALC$_{10\%}$	1.00 ± 0.26	1.39 ± 0.32
PVA05$_{70\%}$+TALC$_{30\%}$	0.89 ± 0.24	1.12 ± 0.20

According to what was observed with reference capsules, no major damages or fractures of the shells were demonstrated upon piercing. In addition, all the items manufactured by IM were characterized

by the formation of similar holes, irrespective of the pierced part (*i.e.* bodies *versus* caps) and of its composition. Specifically, hole diameters in the 0.8-1.5 mm range were obtained, with minor data variability dealing with caps and bodies of analogous composition. As a further note, the PVA-based shells seemed slightly harder to pierce, especially if compared with gelatin capsules, probably for 2 main reasons: *i)* their greater thickness (*i.e.* 600 µm-thick *versus* 50-100 µm thick walls) and *ii)* the presence of the injection point close to the dome of the capsule. This represented the entry point of the molten material into the mold cavity and was positioned at the top of its rounded end for processability reasons. (*i.e.* favor the flow of the melt and filling of the mold cavity). In this respect, once a suitable formulation is identified, both the above described aspects could be easily overcome by designing an appropriate mold.

3.2.3 Moisture barrier

The search for viable alternatives to industry standard capsules, irrespective of the specific application targeted, was primarily promoted by the need for overcoming relevant limitations and/or implementing novel properties. In this respect, availability of a ready-to-use system able to act as a protective barrier to environmental moisture would be of great interest for stability-related reasons. Based on these considerations, the capability of PVA-based molded capsules to act as an effective moisture barrier was worth assessing. Immediately after molding, the water content of the resulting items was particularly low (*i.e.* < 1.5%). To further investigate the tendency of molded shells towards water vapor protection, feasibility of NIR spectroscopy in measuring, in a non-destructive-way, the amount of moisture absorbed by both molded shells and their content was investigated.

In the last years, the application of NIR both at the research level and in actual pharmaceutical production has increased. Indeed, it represents a fast, easy-to-apply and non-destructive tool for in-process, on-line and at-line monitoring controls, as it is virtually applicable to any matrix [De Beer at al., 2011; Grassi et al., 2018; Kirsch et al., 1995]. In this respect, the Food and Drug Administration's Process Analytical Technology initiative, aiming at optimizing the pharmaceutical processes by

reducing the number of offline destructive controls, played a major role in promoting the implementation of NIR technology [Hinz, 2006]. Indeed, the unique combination of bonds in a molecule represents its fingerprint, with NIR very sensitive to any change in the amount or type of bonds in a given sample. As a result, it could be used to monitor the moisture content, the title of a specific component into a powder blend and possible physical modifications undergone by the sample during processing, such as variation in the particle size during wet granulation [Bär et a., 2018].

Borrowing what is widely done when NIR spectroscopy is used as a control tool in film-coating, a mathematical approach was applied, relying on SNV, first derivative, PLS calibration and cross-validation methods. In order to generate a complete pull of data, different samples were kept at pre-defined RH levels. Specifically, free AAP powder and PVA-based capsule shells, both empty and filled with AAP, were stored for 1 month at 40 °C and 55%, 75% and 95% RH. Initially, NIR spectra were acquired on different substrates kept in a single humidity condition, to assess capability of the probe for detecting various materials and data reproducibility. Notably, NIR sensitivity was challenged at increasing levels of complexity, starting from binary systems (*e.g.* AAP powder or void capsules *versus* moisture) up to more complex conditions (*e.g.* AAP within molded shells of different composition *versus* moisture). By way of example, spectra of AAP stored at 75% RH in completely exposed conditions are reported in Figure 5a. The fingerprint profiles generated from different powder samples turned out comparable, highlighting a remarkable reproducibility of NIR acquisition. Moreover, characteristic patterns related to either empty or filled capsules based on PVA03 and PVA05 are summarized in Figure 5b. The data collected demonstrated the NIR ability to discriminate between shells having diverse composition, while the presence of AAP within the capsule seemed to not affect the measurements.

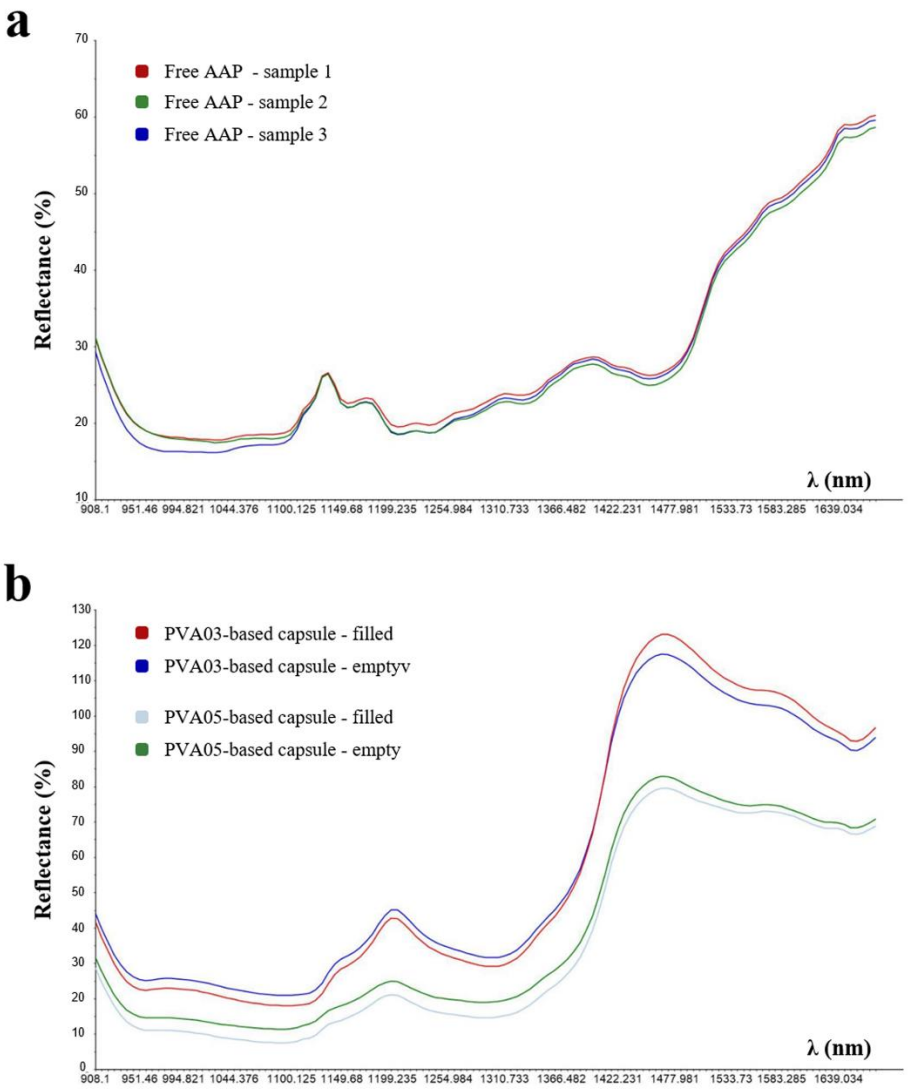


Figure 5: NIR spectra relevant to a) AAP and b) empty as well as filled capsules of different composition stored at 75 RH%.

Finally, PCA analysis was performed on the spectra from specimens maintained at different RH conditions. By ensuring visual representation of the relationships between samples and variables, it would provide useful insights on how the measured variables might cause some samples to appear similar or to result different from each other. In this respect, PCA was a useful way to have a glance on how the process was performing. Indeed, if the data are coherent, it will be possible to highlight an alignment of the points on the PCA chart, indicating that they were following a precise pattern resulting from a physical value alignment, and they were not randomly scattered.

In this respect, three well-defined levels of moisture content were detected. They turned out proportional to the relative humidity of the storage conditions as highlighted, by way of example for AAP powder, in Figure 6.

Therefore, the NIR technology was confirmed able not only to identify different substrates but also to define, with good reproducibility, a moisture trend from samples maintained in diverse conditions.

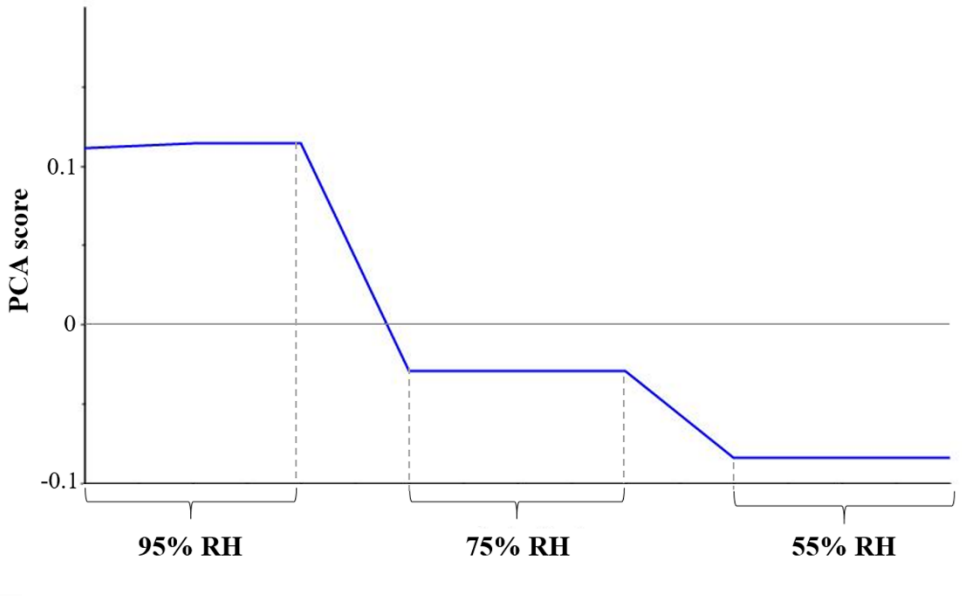


Figure 6: PCA results relevant to free AAP kept at different humidity conditions

Based on the previously built calibration curves, the moisture contents of different samples were determined (Figure 7). In particular, the specimens analyzed were: free AAP, molded shells based on different PVAs and AAP removed from such capsules. In addition, the NIR data were checked against the results attained from repeated LOD experiments and no major difference were highlighted (discrepancy ≤ 2%).

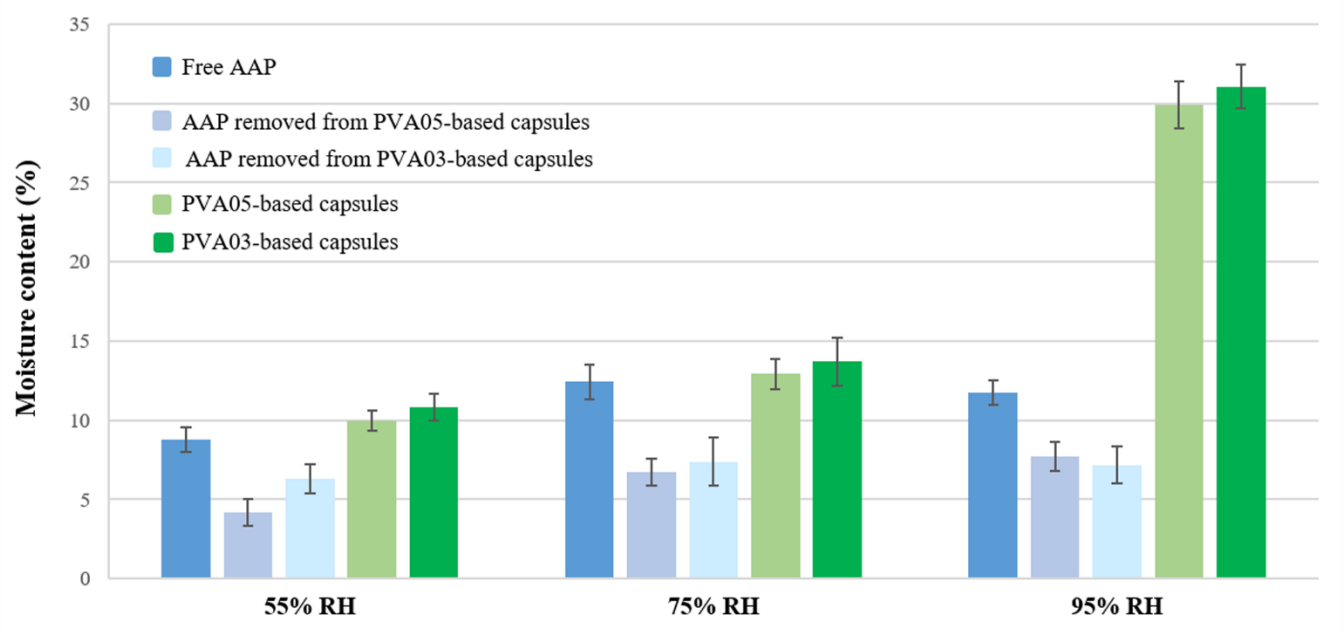


Figure 7: moisture content data relevant to different samples

Irrespective of the RH conditions considered, molded PVA-based capsular devices showed an increase humidity content. However, they were able to protect their filling. Indeed, the AAP contained in such shells always pointed out a moisture content that, at all the RH values investigated, was half of that relevant to free AAP. Notably, while PVA05 seemed to offer a slightly better protection at 55% RH compared to PVA03, their behavior resulted similar at higher RH conditions.

4. Conclusions

In this work, the development of novel capsules that could be mass-manufactured and would serve as an alternative to gelatin- and HPMC-based shells currently on the market was studied. Indeed, widening the portfolio of available capsules would not only reduce possible incompatibility issues, but also overcome risks of allergies and intolerances, while respecting religious restrictions and dietary habits users may have. At the same time, such an approach could help to overcome the drawbacks associated with gelatin shells, *i.e.* lacking in moisture protection. Indeed, having moisture-

protective capsules could be particularly advantageous when dealing with filling formulations whose stability is strongly affected by changes in the water content of the environment, such as those administered *via* DPIs. In this respect, feasibility of IM in the production of PVA-capsules was here demonstrated. The resulting prototypes pointed out good weight and thickness reproducibility and a broad range of performances, that ranged from immediate to pulsatile release. In addition, molded capsules exhibit a piercing behavior that turned out suitable for their use in DPIs, together with an interesting ability to protect the filling from water vapor sorption, which was assessed taking advantage of a non-destructive spectroscopic method. Overall, the results obtained in this work - especially the potential for moisture protection combined with the other advantages provided by the selected manufacturing technique (*e.g.* design versatility, continuous and quick manufacturing, low energy consumption) - could expand the application opportunities for molded capsules bringing, in the long-term, a new ready-to-fill option on the market.

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Figure 1 revised

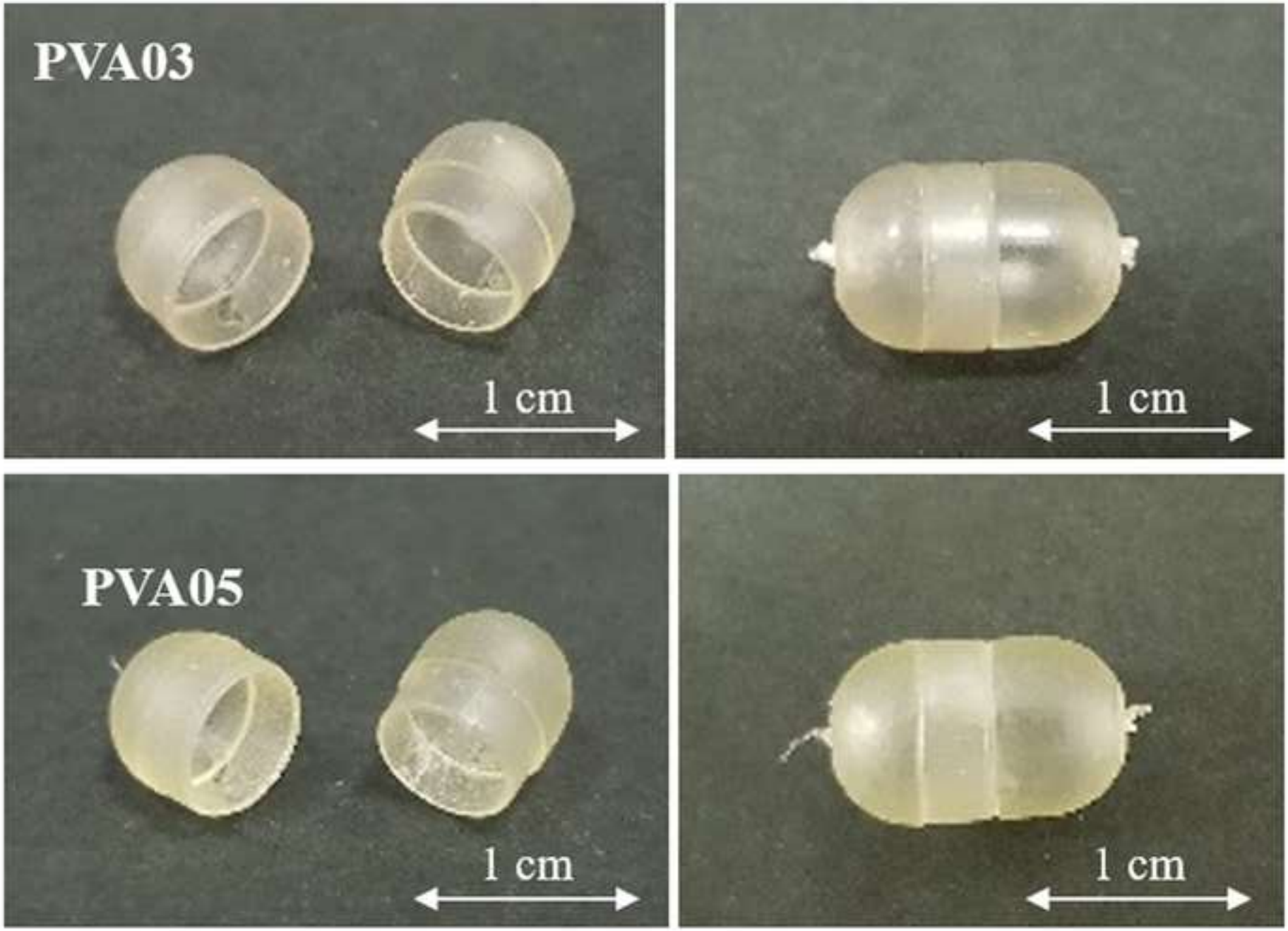


Figure 2 revised

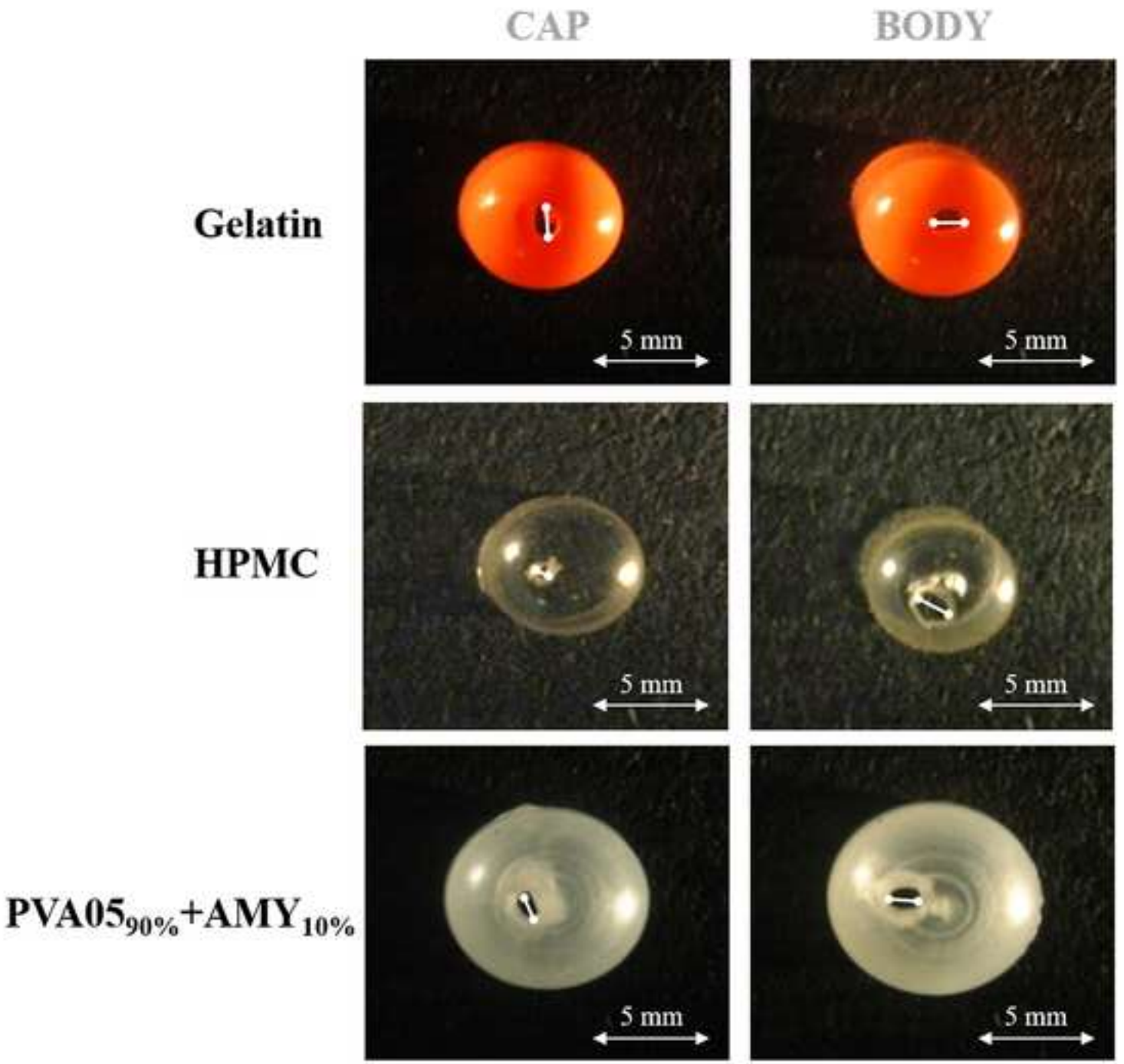
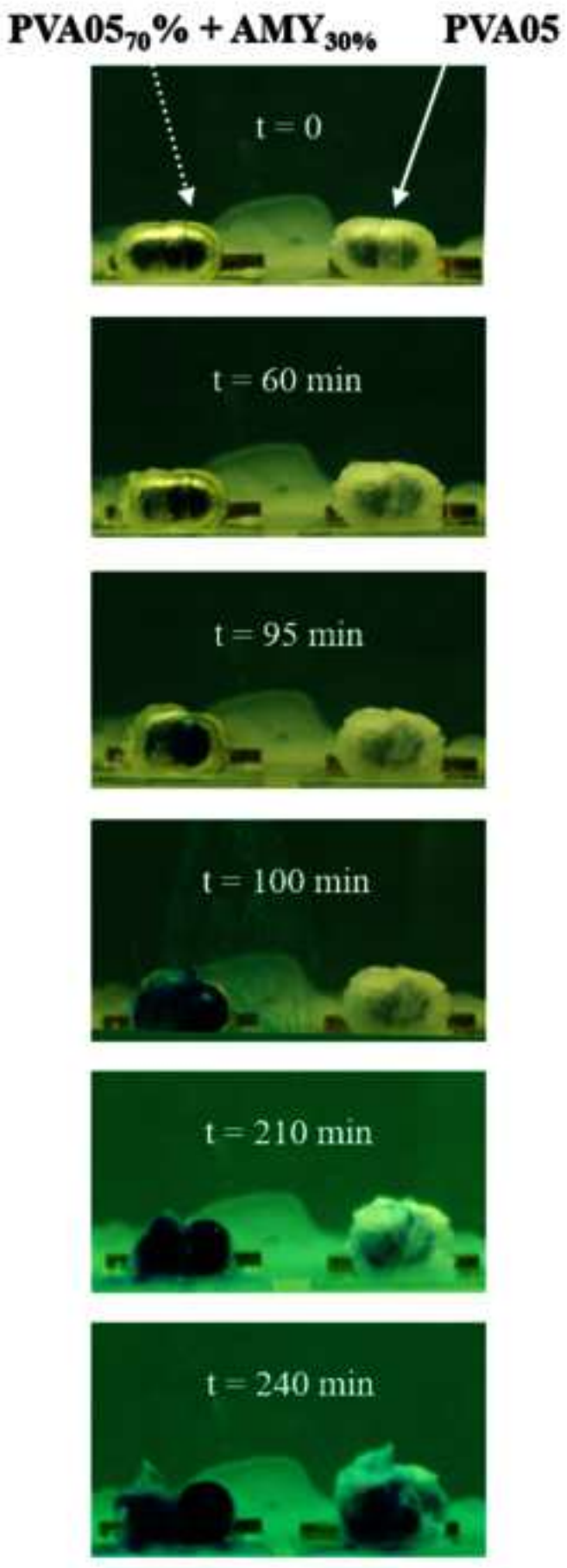


Figure 3


PVA05$_{70}$% + AMY$_{30\%}$
PVA05
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t = 95 min
t = 100 min
t = 210 min
t = 240 min

Figure 4 revised

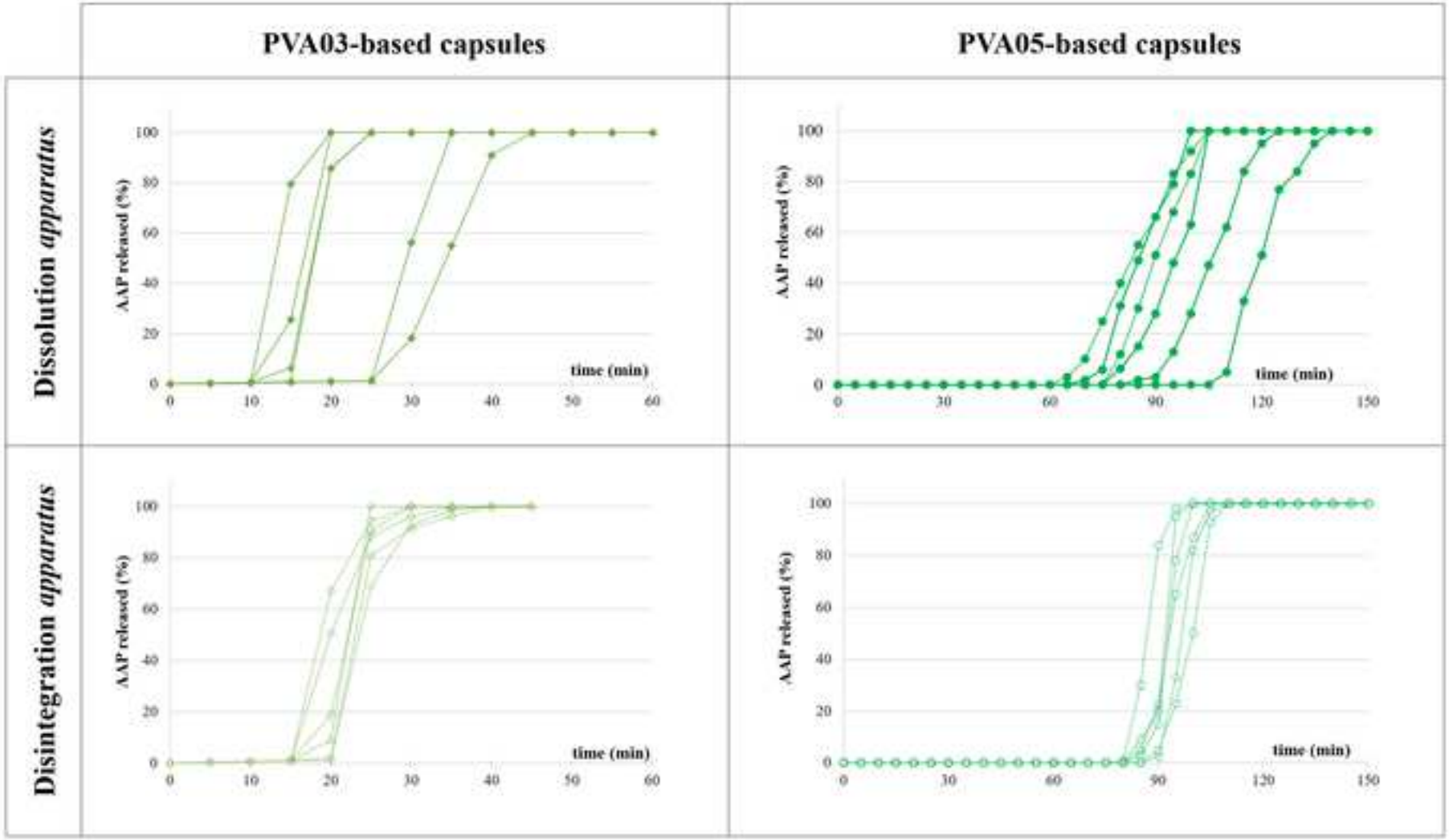


Figure 5 revised

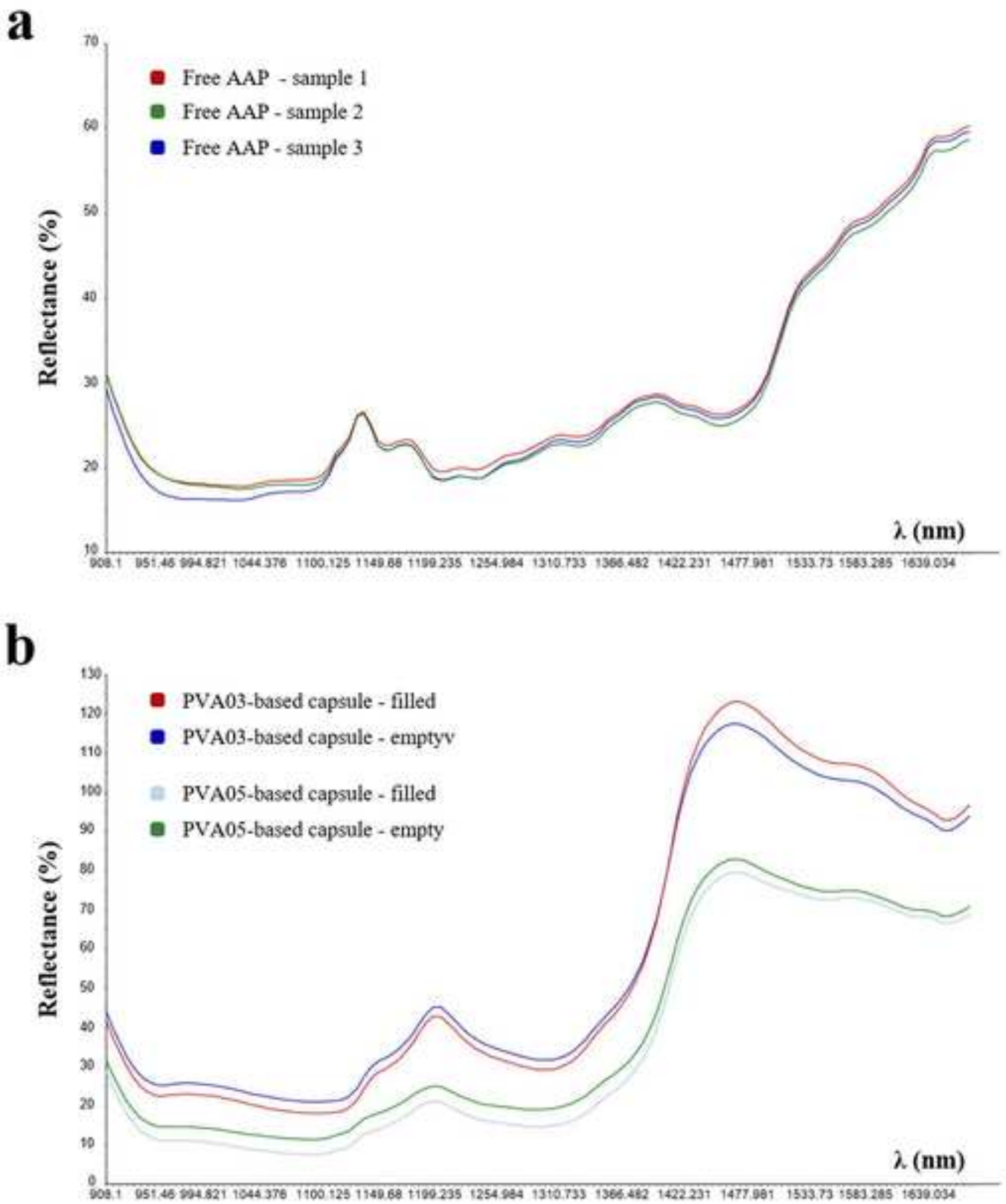


Figure 6 revised

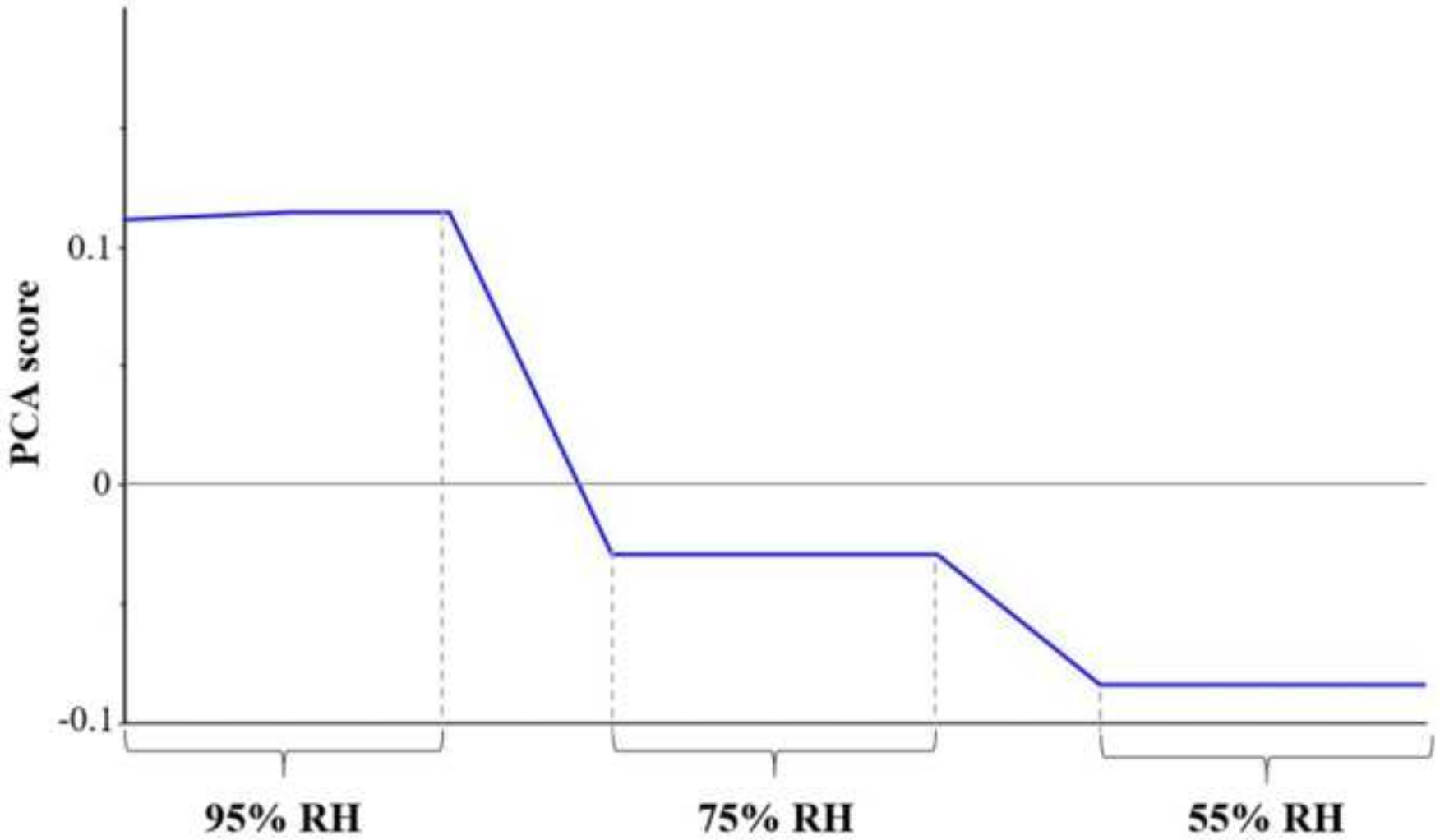
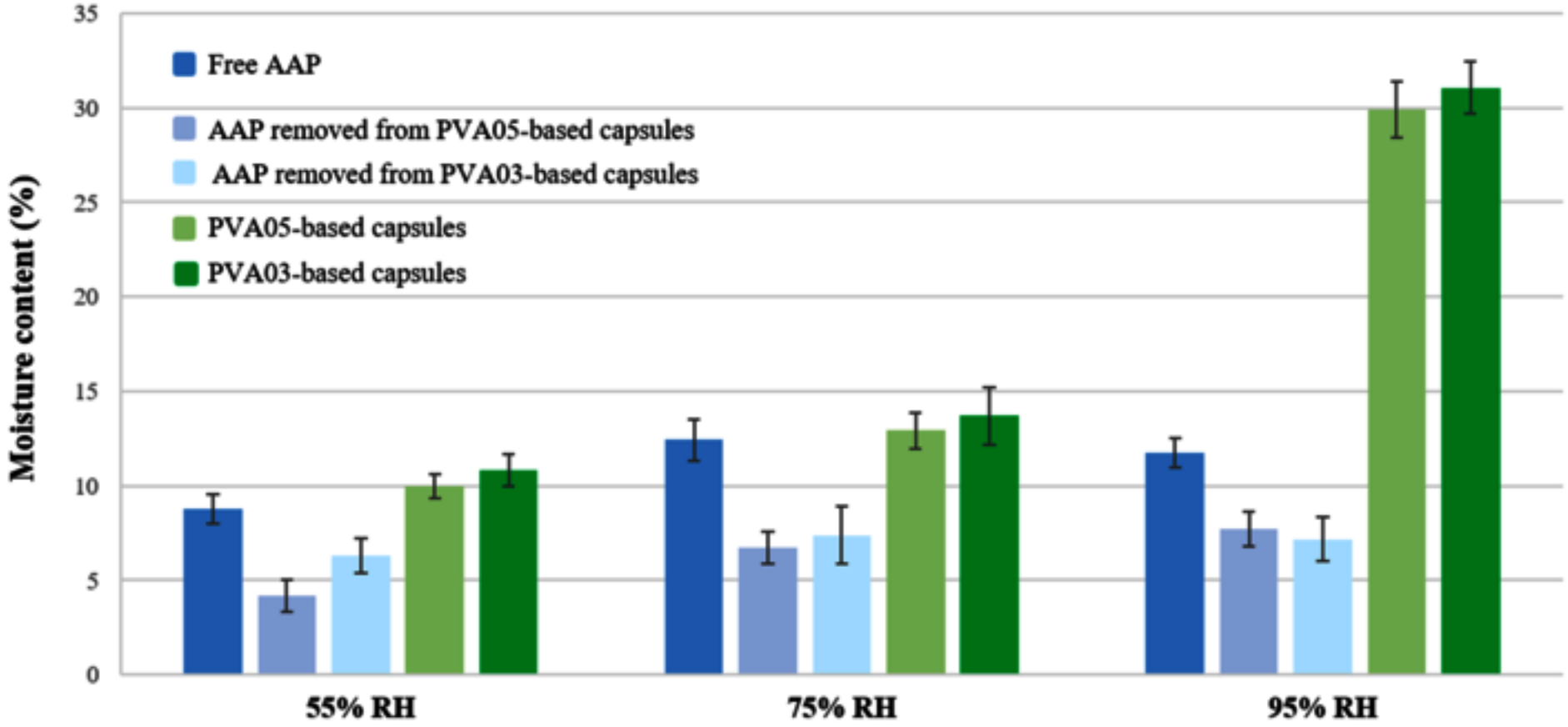


Figure 7


Moisture content (%)
35
30
25
20
15
10
5
0
Free AAP
AAP removed from PVA05-based capsules
AAP removed from PVA03-based capsules
PVA05-based capsules
PVA03-based capsules
55% RH
75% RH
95% RH