

1 **ERODIBLE DRUG DELIVERY SYSTEMS FOR TIME-CONTROLLED**

2 **RELEASE INTO THE GASTROINTESTINAL TRACT**

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4 Alessandra Maroni, Lucia Zema, Matteo Cerea, Anastasia Foppoli, Luca Palugan,

5 Andrea Gazzaniga*

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7 Università degli Studi di Milano, Dipartimento di Scienze Farmaceutiche, Sezione di

8 Tecnologia e Legislazione Farmaceutiche "Maria Edvige Sangalli", Via G. Colombo 71,

9 20133 Milan, Italy.

10 *Corresponding Author: andrea.gazzaniga@unimi.it, phone +39 02 503 24654

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12

13 **Abstract**

14 In oral delivery, lag phases of programmable duration that precede drug release may
15 be advantageous in a number of instances, e.g. to meet chronotherapeutic needs or
16 pursue colonic delivery. Systems that give rise to characteristic lag phases in their
17 release profiles, i.e. intended for time-controlled release, are generally composed of a
18 drug-containing core and a functional polymeric barrier. According to the nature of the
19 polymer, the latter may delay the onset of drug release by acting as a rupturable,
20 permeable or erodible boundary layer. Erodible systems are mostly based on water
21 swellable polymers, such as hydrophilic cellulose ethers, and the release of the
22 incorporated drug is deferred through the progressive hydration and erosion of the
23 polymeric barrier upon contact with aqueous fluids. The extent of delay depends on the
24 employed polymer, particularly on its viscosity grade, and on the thickness of the layer
25 applied. The manufacturing technique may also have an impact on the performance of
26 such systems. Double-compression and spray-coating have mainly been used, resulting
27 in differing technical issues and release outcomes. In this article, an update on delivery
28 systems based on erodible polymer barriers (coatings, shells) for time-controlled release
29 is presented.

30

31 **Keywords**

32 Oral pulsatile release, Oral colon delivery, Coating, Swellable/erodible hydrophilic
33 polymers, Injection-molding, Fused deposition modeling 3D printing.

34

35 **Introduction**

36 Oral delivery systems for time-controlled release are able to defer the onset of drug
37 release into the gastrointestinal tract for a programmable lag period independent of pH,
38 ionic strength, enzyme concentration and other physiological parameters. It is by now
39 recognized that a delay prior to release may be advantageous for effective
40 pharmacological treatment of several pathologic conditions [1]. This is typically the
41 case with a variety of high-morbidity rheumatic, cardiovascular and respiratory chronic
42 diseases, which show cyclic patterns in their signs and symptoms [1,2]. When these
43 mainly recur at night or in the early morning hours, bedtime administration of drug
44 products having a proper lag phase in their release profile would help provide
45 pharmacological protection as needed. On the other hand, both untimely awakenings, as
46 an immediate-release dosage form would require, and exposure to unnecessarily
47 sustained therapeutic drug levels, as prolonged-release formulations taken before sleep
48 would entail, could thereby be overcome. As a result, not only the efficacy and safety of
49 a treatment but also the relevant patient compliance may greatly be enhanced through
50 the use of chronopharmaceutical delivery systems.

51 Besides, a lag phase prior to release allows to target the colonic region with drug
52 molecules intended for either a local action, e.g. to treat Inflammatory Bowel Disease
53 (IBD), or for systemic absorption, especially of biotech molecules that pose stability
54 issues in the proximal gut and may benefit from the aid of enhancers for mucosal
55 permeation [3,4]. When colon delivery is sought, the lag phase is expected to last
56 throughout the entire small intestinal transit ($3 \text{ h} \pm 1 \text{ SD}$), which was reported not to be
57 strongly influenced by the characteristics of dosage units and by food intake [5,6].
58 Moreover, the lag period should be started upon emptying from the stomach rather than

59 on administration, owing to the high variability of gastric residence that cannot reliably
60 be predicted. Hence, in order to attain colonic release based on a time-controlled
61 approach, enteric coating is generally required.

62 Repeated lag phases, each followed by the release of a drug dose fraction, may be
63 exploited to fulfill multiple daily administrations regimens when prolonged release is
64 not a viable option, e.g. because of pharmacokinetic (strong first-pass effect) or
65 pharmacodynamic (tolerance) constraints. Successive release pulses are also proposed
66 as an alternative strategy in antibiotic therapy, possibly resulting in restrained growth of
67 resistant bacterial strains [7].

68 Finally, properly modulated lag phases prior to the release of co-administered
69 bioactive compounds may avoid undesired drug-drug interactions in the gastrointestinal
70 tract and overcome the need for differing dosing schedules, thus improving the overall
71 patient convenience and compliance [8].

72 Peroral delivery systems for time-controlled release are expected to yield lag phases
73 on the order of few hours, which may be consistent with their mean residence time
74 within the digestive tract. These are often pursued through functional polymeric barriers
75 that enclose an inner drug formulation [9,10]. According to the physico-chemical
76 properties of their polymeric components and type of excipients added (plasticizers,
77 pore formers, bulking agents), such barriers delay the onset of release via differing
78 mechanisms. They may indeed undergo time-programmed disruption, become leaky or
79 be subject to progressive erosion/dissolution. In particular, erodible systems are
80 generally single-unit dosage forms based on a drug containing-core, such as an
81 immediate-release tablet or capsule, and a swellable hydrophilic barrier of adequate
82 thickness and polymer viscosity. Such a barrier may be a coating or, in more recent and

83 innovative instances, a freestanding release-modifying shell available for filling with
84 any drug formulation.

85 Because of the inherent safety and biocompatibility profile as well as of their
86 availability in a range of grades and reasonable costs, hydrophilic cellulose derivatives,
87 namely hydroxypropyl methylcellulose (HPMC) and, less frequently, hydroxypropyl
88 cellulose (HPC) and hydroxyethyl cellulose (HEC), are broadly used as the functional
89 polymers in erodible delivery systems [11]. Other polysaccharides, including
90 galactomannans, alginates, xanthan gum, and non-saccharide hydrophilic polymers,
91 such as polyvinyl alcohol (PVA) and polyethylene oxide (PEO), are nonetheless also
92 employed. All of these materials are largely utilized in the food, pharmaceutical,
93 nutraceutical and cosmetic industries mainly as rheology-modifiers, stabilizers, binders
94 and film-coating agents.

95 Upon water uptake, such polymers typically go through a glassy-rubbery
96 thermodynamic transition that is associated with distension and disentanglement of their
97 macromolecular chains [12-14]. Consequently, the polymer structure may expand, erode
98 due to mechanical attrition and/or dissolve at a rate that chiefly depends on the relevant
99 physico-chemical characteristics and on the ionic strength and temperature of the
100 medium. As the aqueous fluid penetrates into the polymeric layer, a swelling front, i.e.
101 the boundary between the glassy and the rubbery domain, and an erosion front, at the
102 interface between the rubbery polymer and the outer medium, are identified. Depending
103 on the relative movements of the swelling and erosion fronts, which in turn are
104 governed by the hydration, dissolution and viscosity properties of the polymer, a gel
105 layer of varying thickness is formed.

106 In a few instances, insoluble materials are added to the hydrophilic polymers to
107 modulate the degree of hydration of the barrier, or even used as the main components of
108 mechanically erodible coatings. In the latter case, their erosion in aqueous fluids would
109 need to be promoted by surfactant excipients.

110 Drug release from hydrophilic erodible systems is in principle deferred until the
111 entire polymeric layer is in the swollen state, i.e. when the swelling front has reached
112 the drug core, possibly followed by extensive dissolution/erosion of the hydrated
113 polymer. The duration of the lag phase is indeed dictated by the physico-chemical
114 properties of the polymer employed, primarily molecular weight and degree of
115 hydrophilicity, and by the thickness of the erodible barrier. The manufacturing
116 technique, which may range from double-compression and spray-coating to hot-
117 processing, can also affect the layer functionality.

118 In the following sections, oral delivery systems for time-controlled release provided
119 with an erodible polymer barrier are reviewed, and advances in this particular field are
120 illustrated with special emphasis on formulation and performance issues.

121

122 **Erodible systems manufactured by double-compression**

123 The manufacturing of oral delivery systems provided with erodible coatings dates
124 back to the early 90s. Until then, the use of such polymers in the manufacturing of solid
125 dosage forms was tied to tableted hydrophilic matrices for prolonged release. Indeed,
126 double-compression technique, also known as press-coating, was adopted in all initial
127 attempts. The first one concerned a three-layer tablet system that was proposed for two-
128 pulse release of drugs [15,16]. Such a system was composed of two conventional drug
129 (ibuprofen) layers and a high-viscosity HPMC (Methocel[®] K4M and Methocel[®] K15M)

130 barrier in between. An impermeable ethylcellulose (EC) film covered the lateral area
131 and one of the bases of the assembly so that the outer surface of a single drug layer was
132 allowed to interact with solvent upon first contact with the medium. The former dose
133 fraction was thereby released, whereas the latter was released after a lag phase due to
134 the hydration and erosion of the polymer barrier. The delay between the release pulses
135 depended on the viscosity of the polymers employed, and release of the latter dose
136 fraction was slower. This was ascribed to a less efficient activation of the disintegrant
137 incorporated within the inner drug layer that was progressively exposed to the aqueous
138 fluid. The release behavior observed *in vitro* was reflected in two-peak plasma
139 concentration curves in healthy volunteers. However, because of its multiple-layer
140 configuration and the need for a partial coating, the system would involve serious
141 scalability issues. Therefore, a simpler press-coated formulation was designed, wherein
142 the polymer, a low-viscosity HPMC (Methocel[®] K100 LV), covered the entire surface
143 of the core [17]. The coated system could yield single-pulse release after a lag phase or,
144 administered in combination with an immediate-release tablet, the repeated release
145 performance attained from the previous device. In the double compression process,
146 positioning of the core tablet in the die represented a critical step. However, by correctly
147 centering it within the polymer powder bed, biconvex tablets with coatings of
148 homogeneous thickness were obtained. As desired, the *in vitro* release was delayed for a
149 reproducible period of time, although leaching of a small percentage of the drug content
150 prior to the quantitative release phase was inferred from the curves. This was ascribed to
151 premature outward diffusion of dissolved drug molecules through the swollen polymer
152 coating.

153 A low- and a high-viscosity HPMC grade (Methocel[®] K100 and Methocel[®] K4M)
154 were used, either alone or mixed with each other, as the coating agents of a delivery
155 system containing ibuprofen, aimed at the chronotherapy of rheumatoid arthritis, or
156 pseudoephedrine hydrochloride, a water-soluble model drug [18-20]. Increasing the
157 coating level or the amount of high- vs low-viscosity polymer resulted in longer lag
158 times and slower *in vitro* release as well as decreased absorption rates in healthy
159 volunteers. Sodium alginate, as compared with HPMC, performed as a less effective
160 barrier-forming polymer. Incorporation of a fraction of the drug dose in the coating
161 layer changed the release behavior, generally yielding biphasic kinetics that depended
162 on the composition of the polymeric coat and its drug load.

163 High-viscosity HPMC (Methocel[®] K4M, Methocel[®] K15M and Methocel[®] K100M)
164 was employed to prepare a system intended for colonic delivery of the anti-parasitic
165 drug tinidazole [21]. An enteric coating was applied externally to enable site-selective
166 release. The lag phase duration and the release rate were markedly affected by the
167 viscosity grade of the polymer, while hardness of press-coated tablets in a 40-60 N
168 range did not impact on the relevant performance. Administered to 2 healthy volunteers,
169 the system was shown to disintegrate in the ascending colon. Methocel[®] K100M was
170 also used to coat, at a compression force of 60-80 N, minitab[®]let cores (3 mm in
171 diameter) intended for immediate or prolonged release of nifedipine [22]. By combining
172 differing core and coated formulations in a gelatin capsule, a variety of release patterns
173 were achieved.

174 Low-viscosity HPMC coatings were applied by an alternative tableting method
175 (One-Step Dry-Coated, OSDRC) based on the use of a specially modified equipment,
176 which was previously set up in order to overcome disadvantages typically encountered

177 with conventional double-compression technique [23]. These mainly encompass the
178 need for poorly scalable multiple-step processing, the issue of coat thickness
179 homogeneity and difficulties in attaining relatively low coating levels. By the OSDRC
180 method, layers of 0.5-2 mm were obtained, with satisfactory thickness homogeneity and
181 practically unchanged performance within a 100-200 MPa range of compression
182 pressure.

183 High-viscosity HPMC was mixed with polyvinylpyrrolidone (PVP) at different ratios
184 and applied, by conventional double-compression technique, to minitabiet cores
185 containing solid felodipine/PVP dispersions [24,25]. Mixing with PVP at 30-50%
186 resulted in improved mucoadhesion of the HPMC coating. The delays prior to a rapid
187 release of the drug increased in duration with the percentage of HPMC in the
188 formulation. *In vitro* delays of more than 10 h were observed with amounts of HPMC at
189 which mucoadhesive properties were enhanced. The issue of possible inconsistency
190 between duration of the lag phase and gastrointestinal transit was faced by the design of
191 a floating pulsatile delivery system aimed at gastro-retention [26]. For this purpose, a
192 verapamil hydrochloride tablet was first coated with low-viscosity HPMC (Methocel[®]
193 E5, Methocel[®] E15 or Methocel[®] E50), expected to defer the onset of drug release. A
194 blend of a high-viscosity grade of the polymer (Methocel[®] K4M) and Carbopol[®] 934P,
195 which also contained sodium bicarbonate to generate effervescence, was subsequently
196 applied to a single face of the unit coated with low-viscosity HPMC. The system was
197 proved able both to delay the onset of release and to float *in vitro*. Lag time depended
198 on the viscosity and amount of HPMC in the coating. A γ -scintigraphic evaluation in 6
199 healthy volunteers highlighted the extended gastric residence of the dosage form and
200 reproducible lag phases before release. In all cases, this occurred in the stomach or

201 small intestine. Recently, various grades of HPMC were used to coat tablet cores based
202 on drugs with differing solubility values [27]. Poorly soluble carbamazepine was
203 released in a pulsatile fashion after erosion of the coating polymer, and the viscosity
204 characteristics of the latter strongly impacted on the relevant performance. On the other
205 hand, more soluble drugs were released in a sigmoidal mode, which was attributed to
206 their diffusion through the fully hydrated HPMC layer, and a poor influence of the
207 polymer viscosity was noticed. The outward diffusion of the drug prior to its
208 quantitative release could be prevented by inserting an enteric film below the erodible
209 coating. However, this would ultimately impart pH-dependence to the lag phase and
210 possibly hamper a timely release of the drug for chronotherapeutic purposes. The
211 amount of HPMC also affected the time and rate of release.

212 Although HPMC was most widely utilized as a coating agent intended for delaying
213 drug release, the use of other hydrophilic cellulose derivatives was reported. Particularly,
214 HPC was the component of a compressed shell that was separately prepared and, once
215 perforated, manually assembled with a cylindrical core tablet containing isosorbide-5-
216 nitrate [28]. The upper and lower bases of the resulting system were coated with an
217 impermeable ethylene vinyl acetate copolymer film. Release was deferred until the
218 polymeric shell was completely eroded or detached. Lag time was affected by the
219 thickness of such a shell and by the composition of the core. Indeed, replacing
220 microcrystalline cellulose with lactose shortened the lag phase because of the osmotic
221 effect exerted by the latter filler.

222 A diltiazem hydrochloride system based on HPC was prepared by conventional
223 press-coating [29,30]. As with HPMC, the lag phase duration was modulated either by
224 increasing/decreasing the amount of coating material applied or by employing HPC, or

225 mixtures thereof, with differing viscosity values. Prototype formulations having *in vitro*
226 delays of approximately 3 h and 6 h were administered to beagle dogs. A good
227 agreement was found between *in vitro* and *in vivo* data relevant to the former prototype,
228 whereas lag time *in vivo* was shorter than *in vitro* in the latter case. This gap was
229 reduced when a paddle rotation speed of 150 rpm was set instead of 100 rpm during
230 release testing. In order to assess its potential for colon delivery, the system having lag
231 time of 3 h was provided with an enteric HPMCAS film containing a gastric emptying
232 marker (phenylpropanolamine hydrochloride) [30]. The mean difference between the
233 time of first appearance in plasma (TFA) of the drug and of the marker molecule was of
234 about 3 h, which was consistent with the lag time obtained from the pH 6.8 fluid stage
235 of the *in vitro* test. HPC was also used in admixture with EC at a weight ratio of 7:1
236 [31]. The addition of the insoluble polymer aided a faster release of aceclofenac,
237 intended for the chronotherapy of rheumatic morning pain, after the delay period. The *in*
238 *vitro* performance of press-coated systems based on this blend was proved independent
239 of various parameters, such as the compression force, paddle rotation speed during
240 release testing and pH of the medium. Provided with an enteric-coating, the formulation
241 was administered to rabbits, showing a clear lag phase as opposed to an immediate-
242 release tablet. However, due to variable residence of solid dosage forms in the stomach,
243 gastroresistance may prevent the anti-inflammatory drug from being released at the time
244 the disease symptoms occur.

245 Low-substituted HPC (L-HPC), an insoluble swellable hydrophilic cellulose ether
246 that is largely used as a disintegrant, was mixed with glyceryl behenate at differing
247 ratios and subjected to a melt-granulation process [32]. The resulting granules were
248 applied by double-compression to theophylline tablet cores to give the erodible layer.

249 The press-coated tablet was studied *in vitro* and in beagle dogs, by pharmacokinetic as
250 well as γ -scintigraphic techniques. Lag phases were reproducible in duration and
251 increased with the amount of glyceryl behenate in the coating formula up to 75%. No
252 significant differences were found either between *in vitro* and *in vivo* lag times, or
253 between *in vivo* lag and disintegration times, both in the fasted and fed state.

254 Press-coated tablets for chronotherapeutic purposes were prepared from HEC
255 employed as the erodible barrier-forming material [33]. The onset of release of
256 diltiazem hydrochloride from the core was delayed *in vitro* as a function of the coating
257 level and the viscosity grade of HEC. The particle size of the polymer also affected lag
258 time. Using powders with larger particle dimensions was associated with shorter delay
259 phases, which was ascribed to the positive effect of a greater porosity on the polymer
260 hydration process. The role played by HEC viscosity was studied in healthy volunteers
261 [34]. When this parameter increased, progressively longer lag time (T_{lag}) and lower
262 maximum concentration (C_{max}) values were observed in the plasma concentration vs
263 time curves. However, the area under the curve ($AUC_{0-24\ h}$) did not change significantly.
264 *In vitro* and *in vivo* lag times were in agreement.

265 Besides cellulose derivatives, the use of PEO as a hydrophilic erodible coating agent
266 was reported. Blended with PEG 6000 at 1:1, it was applied to tablets containing
267 acetaminophen and differing water soluble excipients, such as PEG 6000, sucrose and
268 lactose [35]. These were added in order to promote erosion of the core in the distal
269 intestine, where the press-coated tablets would be intended to release their drug load,
270 thus possibly counterbalancing the paucity of water of regional fluids. The core erosion
271 was experimentally quantified and expressed by a purposely introduced parameter, i.e.
272 the core erosion ratio. In a pharmacokinetic study conducted with fasted beagle dogs,

273 greater C_{\max} and AUC values were obtained from formulations having a higher core
274 erosion ratio. The amount of PEG 600 vs PEO was raised up to 5:1 in the coating of
275 nifedipine tablets containing sucrose as an erosion enhancer [36]. *In vitro* lag times
276 increased with the percentage of PEO and were aligned with TFA data in beagle dogs.
277 PEO formed the swelling/erodible upper layer of a press-coated system with an
278 impermeable cellulose acetate propionate shell covering one of the bases and the lateral
279 surface [37]. The amount of polymer in the top coating affected both the time and rate
280 of release of drug molecules with different solubility. Visual monitoring of
281 morphological changes undergone by the system during *in vitro* testing highlighted
282 gradual expansion and erosion of the partial PEO coat until final detachment from the
283 underlying unit. Used in place of PEO, sodium alginate and sodium
284 carboxymethylcellulose had less and greater impact on the release performance,
285 respectively, consistent with their observed swelling/erosion behavior. Guar gum having
286 ten-fold higher viscosity than PEO also exerted a tighter control of the onset and rate of
287 release [38]. Increasing the core diameter or adding a soluble filler, such as lactose, to
288 PEO or guar gum top layers resulted in reduced duration of the lag phase and enhanced
289 release rate. Differing PEO grades were employed to coat tablets containing solid
290 dispersions of indomethacin in a novel sucrose fatty acid ester carrier [39]. *In vitro* lag
291 time depended on the viscosity and amount of the coating polymer. In 6 healthy
292 volunteers, press-coated tablet systems with *in vitro* lag phase of approximately 6 h
293 brought about delayed appearance of indomethacin in plasma with respect to an
294 immediate-release commercial product. However, no significant differences were found
295 in the C_{\max} and AUC relevant to the two formulations.

296 Hydrophilic polymers of natural origin were also proposed as press-coating agents
297 for time-controlled delivery systems. For instance, powders composed of sodium
298 alginate and chitosan, forming a polyelectrolyte complex, and of lactose as a filler were
299 obtained by spray-drying, evaluated for flowability and compaction properties and
300 finally applied to acetaminophen tablets [40]. Through progressive erosion of the
301 coating layer, drug release was delayed in pH 6.8 fluid for a time interval that depended
302 on the chitosan content of the composite powder and on the polymer degree of
303 deacetylation. A prompt release phase was eventually observed. In pH 1.2 fluid,
304 acetaminophen was released slowly after longer delays. Prepared for comparison
305 purposes, physical mixtures of chitosan with spray-dried alginate/chitosan particles and
306 spray-dried powders composed of lactose and of pre-formed alginate/chitosan complex
307 failed to provide the desired release pattern.

308 Blends of the bacterial exopolysaccharide xanthan gum and plant galactomannan
309 locust bean gum were used in the double-compression coating of the SyncroDose™
310 delivery system according to TIMERx® technology [41]. Differing release modes and
311 lag times were achieved by modifying the concentration and ratio of the two
312 polysaccharides, performing as synergistically interacting heterodisperse polymers.

313

314 **Erodible delivery systems manufactured by spray-coating**

315 The feasibility of coating techniques other than double-compression was explored for
316 the manufacturing of erodible polymer barriers able to control the onset of drug release.
317 Particularly, the goals were to establish simpler processing modes, with better industrial
318 scale-up prospects, exploit conventional production equipment and broaden the range of
319 viable core formulations (e.g. large tablets, minitables, granules, pellets, gelatin

320 capsules) [17]. Furthermore, some performance issues, strictly connected with the
321 structure of press-coatings, their relatively high thickness and the relevant homogeneity
322 limitations, needed to be improved. These primarily involved extended, variable and
323 poorly flexible lag times, incomplete suppression of drug leakage during the delay
324 period and impact on the subsequent release phase. Preliminary spray-coating trials
325 were thus undertaken because such a technique would have allowed continuous and
326 uniform films to be formed rather than layers of pressed powder, and fluid bed as well
327 as rotating pan equipment to be utilized instead of specially devised or modified
328 tableting machines [17,42,43]. In addition, it could in principle be adapted to substrate
329 dosage forms having diverse size, surface and density characteristics, thereby
330 circumventing the dimensional and mechanical constraints associated with double-
331 compression. A limited technical background was available on the use of swellable
332 hydrophilic polymers as film-coating agents, and this mainly concerned application of
333 low-viscosity grades as thin layers with protective, taste-masking or cosmetic function.
334 Nonetheless, HPMC with marked viscosity (Methocel[®] K4M and Methocel[®] K15M)
335 appeared potentially suitable for delaying drug release for a time interval on the order of
336 hours without binding to excessively thick coatings. The polymers were suspended in a
337 hydro-alcoholic vehicle in order to counteract the thickening effect they exert upon
338 hydration. The ratio between ethanol and water needed to be adjusted so as to enable
339 nebulization of the coating suspension at reasonable rates and polymer concentrations
340 on the one hand, and adequate coalescence of the solid particles on solvent evaporation
341 on the other. The addition of plasticizing, anti-tacking and binding excipients, such as
342 PEG 400, talc and PVP, was investigated. The coatings applied to tablets and
343 minitables were provided with consistent thickness and smooth surface. Moreover, they

344 yielded the desired release pattern. Considering the regulatory issues raised by organic
345 solvents, the feasibility of aqueous spray-coating by fluid bed was then evaluated using
346 HPMC having increasing viscosity, namely Methocel[®] E5, Methocel[®] E50 and
347 Methocel[®] K4M [44-46]. The operating conditions, above all spray rate, inlet air
348 temperature and polymer concentration in the solutions, required an attentive set-up in
349 order to overcome major problems of powdering and nozzle clogging as well as lengthy
350 processing. The viscosity grade of the polymer chiefly affected the process time,
351 nebulization being possible only with diluted solutions that increased the spraying and
352 drying duration. From all of the polymers under investigation, coated units with
353 satisfactory physico-technological characteristics were obtained. The release behavior
354 was studied by paddle dissolution and modified disintegration apparatus. The latter
355 proved indeed better suited to prevent sticking of swollen HPMC to the vessels, thus
356 providing more reliable data. By both testing methods, a prompt release after a lag
357 phase was highlighted, which depended on the coating level and the polymer viscosity.
358 Using Methocel[®] E50 resulted in acceptable process feasibility, ability to delay drug
359 release and fine-tuning of the lag phase. Moreover, the coating process was shown
360 robust and potentially scalable. In the case of Methocel[®] K4M, not only the coating
361 operations were strongly impaired by the high viscosity of water solutions, but also a
362 small amount of drug was slowly released from coated units toward the end of the delay
363 period. This was attributed to the formation of a firm, poorly erodible gel structure
364 ultimately rupturing with the aid of the inner tablet disintegration upon water influx
365 [47]. When the Methocel[®] E50-based coating procedure was applied to hard- and soft-
366 gelatin capsules instead of tablets, the process parameters needed to be adjusted in order
367 to prevent the sticking and shrinking of the shells [48]. In order to streamline

368 manufacturing of Methocel[®] E50-coated systems, alternative techniques, such as
369 tangential-spray film-coating and powder-layering carried out by fluid bed
370 rotogranulator, were attempted. Preliminary studies in volunteers demonstrated that,
371 irrespective of the core dosage form, delivery systems coated with Methocel[®] E50 by
372 aqueous spray-coating were able to defer drug appearance in saliva as a function of the
373 coating level [45,48]. The *in vitro* and *in vivo* lag phases were comparable in duration.
374 Moreover, when provided with a gastroresistant film, labeled formulations were shown
375 to consistently break up in the ascending colon. After low-molecular weight drugs,
376 chosen as models because of their stability characteristics and easy analysis, the
377 possibility of conveying bovine insulin by this delivery system was explored [48-52]. In
378 order to increase the chances of preserving integrity of the protein and promoting its
379 permeation through the intestinal mucosa, enzyme inhibitor and absorption enhancer
380 adjuvant compounds were incorporated in the formulation. Insulin was proved to
381 withstand all manufacturing steps, as inferred by assaying the degradation products
382 mentioned by European Pharmacopoeia, and was released *in vitro* in a pulsatile mode,
383 as previously observed with antipyrine and acetaminophen, along with the adjuvants.
384 The latter were also applied as a separate film enclosed between two Methocel[®] E50
385 layers, so that their release would occur earlier than that of the protein drug contained in
386 the core, and less threatening conditions could be established *in vivo* beforehand
387 [53,54].

388 When erodible coatings were applied to minitabket cores, relatively larger amounts of
389 polymer were found necessary than with single units in order to obtain lag times
390 potentially suitable for chronotherapeutic or colonic release purposes [55-57]. Thus, the
391 thickness of the resulting film coatings would ultimately fail to comply with the size

392 requirements of multiple-unit dosage forms. Besides, depending on the viscosity grade
393 of the polymer employed, the rate of release at the end of the lag phase would most
394 likely be reduced. With the aim of overcoming this formulation issue, the external
395 application of an insoluble, flexible and increasingly leaky film was proposed. Such a
396 film was mainly intended to slow the uptake of water by the underlying HPMC layer,
397 and consequently the relevant hydration as well erosion processes, without acting as a
398 major mechanical constraint to the polymer expansion. Eudragit[®] NE 30 D was selected
399 as the film-forming agent, whereas various superdisintegrants, above all Explotab[®] V17,
400 were added as especially effective non-conventional pore formers. After tuning the
401 composition of the outer film and the ration between HPMC and polymethacrylate
402 coating levels, the desired release performance and dimensional characteristics were
403 obtained from formulations based on this novel two-layer design.

404 HPMC barriers derived from coalescence of polymer particles were prepared not
405 only by spray-coating but also by dipping, which circumvented the technical difficulties
406 associated with nebulization of highly viscous polymeric solutions [58]. Ethanol/water
407 mixtures were used to disperse the HPMC powder. Immersion steps, each followed by
408 manual hot-air drying, were repeated until the tablets had reached the established weight
409 gain. The latter was related to the lag phase duration. By affecting the structure of the
410 coat layer, parameters such as the ethanol/water volume ratio, the concentration of the
411 polymer and the time during which it was allowed to swell in the hydro-organic vehicle
412 also impacted on the release of nifedipine from the core tablet.

413 Waxy materials of natural origin, in admixture with a surfactant, were employed as
414 an alternative to swellable hydrophilic polymers in order to attain erodible barriers for
415 time-controlled release [59]. Spraying of water dispersions of such lipophilic coating

416 agents required that the processing temperature be set at relatively high values (75°C).
417 The resulting delivery system (Time Clock[®]) proved suitable for deferring salbutamol
418 sulfate release *in vitro* and in healthy volunteers. In both cases, the lag phases were
419 clearly dependent on the coating level. An agreement between *in vitro* and *in vivo* data
420 was achieved when media having increased viscosity were used for release testing,
421 which led to longer *in vitro* delays. The performance of the system in the
422 gastrointestinal tract was demonstrated not to be influenced by food intake in 6 subjects,
423 and AUC_{0-∞} as well as C_{max} in the fasted state were consistent with those of an
424 immediate-release reference product. The Time Clock[®] system provided time-based
425 colonic delivery in humans when in gastro-resistant configuration, as highlighted by γ-
426 scintigraphy [60]. This was confirmed in 8 fed volunteers through pharmaco-
427 scintigraphic evaluation of a 5-aminosalicylic acid-containing formulation [61].

428

429 **Erodible delivery systems manufactured by hot-processing techniques**

430 Hot-processing techniques, which enable the production of high-density structures of
431 any desired form from softened/melted thermoplastic material substrates, are raising
432 huge interest in every manufacturing area. However, their exploitation in the
433 pharmaceutical field is still fairly limited despite the enormous potential held [62-65]. It
434 is only recently that drug delivery applications mainly of hot-melt extrusion (HME),
435 injection-molding (IM) and three-dimensional (3D) printing by fused deposition
436 modeling (FDM) have been investigated and reported. Interestingly, the use of such
437 techniques was proposed for the production of void functional capsule shells
438 independent of their core units, with considerable prospective advantages from both the
439 technical and the regulatory point of views [66-68]. In this respect, the feasibility of IM

440 in fabrication of erodible shells intended to defer release of their contents was explored
441 [66]. HPC of various viscosity grades was selected as the capsule-forming polymer
442 because of the inherent thermoplastic behavior upon heating. A bench-top IM press was
443 employed, and the design of a specially suited mold was required. Through its use, cap
444 and body items were obtained within single automated production cycles. *In vitro*
445 studies pointed out a rapid release of the model drug after lag times that, composition
446 being equal, correlated with the thickness of shells in the 300-900 μm range
447 investigated. By visual inspection of capsule systems immersed in deionized water, it
448 was inferred that release after the delay phase would be connected with rupturing of the
449 hemispherical top and bottom ends of the device that were thinner than the cylindrical
450 region where cap/body portions overlapped. On administration of these prototypes to 3
451 healthy volunteers, the *in vivo* lag times calculated from salivary concentration curves
452 of acetaminophen were found in linear relationship with the *in vitro* ones [69]. The
453 design of a novel mold for 600 μm thick units and concomitant setting up of proper
454 formulation as well as operating parameters were subsequently undertaken [70]. This
455 allowed faster production cycles to be carried out without adding external or internal
456 lubricants. The shells obtained showed improved mechanical properties, which would
457 aid large-scale filling by the equipment used with conventional gelatin capsules, and
458 less variable thickness that was also closer to the theoretical value. Besides, the issue of
459 thicker body/cap overlap areas was overcome. As a result, more reproducible release
460 profiles were attained. The time to shell opening was demonstrated consistent
461 irrespective of differing types of solid dosage forms conveyed (fine powder, granules,
462 pellets, solid dispersion). These HPC capsules were successfully subjected to enteric
463 coating, with no need for sealing the assembled caps and bodies, and then to final curing

464 [71]. Such systems fulfilled the requirement of resistance in pH 1.2 medium for 2 h,
465 while maintaining the original pulsatile release curves when tested in pH 6.8 phosphate
466 buffer. Accordingly, they appeared potentially suitable for time-dependent colon
467 delivery, provided that the shell thickness be properly modulated so that duration of the
468 *in vivo* lag phase would match the small intestinal transit time.

469 Capsule shells composed of HPC were lately replicated by FDM 3D printing, starting
470 from filaments purposely prepared in-house by HME [68]. After assessing the
471 possibility of attaining hollow structures by the use of FDM and developing the needed
472 computer-aided design (CAD) files, bodies and caps of the shells were manufactured.
473 Overall, these exhibited satisfactory physico-technological characteristics and,
474 assembled into a drug-containing device, the typical lag phase before a rapid and
475 quantitative release. Upon contact with deionized water, the behavior of capsule shells
476 fabricated by FDM was comparable with that of analogous molded systems, thus
477 supporting the real-time prototyping potential of this 3D printing technique and its
478 possible exploitation in formulation development studies aimed at IM production.

479 Based on the expertise gained from the manufacturing of functional capsule shells,
480 cylindrical dosage forms, such as immediate- and prolonged-release polymeric units,
481 were also fabricated by HME and IM [72,73]. The relevant production via hot-
482 processing was found to offer inherent advantages over the established techniques.

483

484 **Conclusions**

485 Drug delivery systems able to incorporate a lag phase of pre-established duration in
486 their release patterns are a topic of high current interest, primarily in connection with
487 oral chronotherapy and colon targeting.

488 Among the numerous formulation strategies proposed, those based on erodible
489 polymeric barriers have largely and successfully been exploited. As the main
490 components of such barriers, swellable/erodible polymers of hydrophilic nature, such as
491 HPMC and other cellulose derivatives, have especially been used. Indeed, they easily
492 enable fine-tuning of the release performance in terms of time and also rate through
493 proper selection of the type and amount of polymer, which will affect the thickness and
494 viscosity of the layer upon hydration. Erodible barriers intended for time-controlled
495 release generally consist in coating layers. These may partially or entirely enclose a
496 drug-containing core thus preventing it from immediately being exposed to aqueous
497 fluids on administration of the dosage form. Coatings may be applied by differing
498 techniques and, accordingly, possess diverse structural and functional characteristics.

499 Apart from coating layers, which are necessarily associated with a specific core
500 formulation, polymeric barriers in the form of erodible shells have recently been
501 manufactured by hot-processing, namely via IM and FDM. Because of the great
502 versatility in terms of design, high innovative content, excellent scale-up prospects and
503 unique benefits related to a separate development as well as production, these capsule
504 shells may open up new ways in the field of time-controlled release and, more broadly,
505 in the oral delivery area.

506

507 **References**

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