

Development of Fixed Dose Combination Products Workshop

Report: Considerations of Gastrointestinal Physiology and Overall Development Strategy

Bart Hens^{1*}, Maura Corsetti^{2,3}, Marival Bermejo⁴, Raimar Löbenberg⁵, Pablo M. González⁶, Amitava Mitra⁷, Divyakant Desai⁸, Dakshina Murthy Chilukuri⁹, Alexis Aceituno¹⁰

¹Department of Pharmaceutical & Pharmacological Sciences, KU Leuven, 3000 Leuven, Belgium

²NIHR Nottingham Biomedical Research Centre (BRC), Nottingham University Hospitals NHS Trust and the University of Nottingham.

³Nottingham Digestive Diseases Centre, School of Medicine, University of Nottingham, Nottingham, UK

⁴Department Engineering Pharmacy Section, Miguel Hernandez University, San Juan de Alicante, 03550 Alicante, Spain

⁵Faculty of Pharmacy & Pharmaceutical Sciences, University of Alberta, Edmonton, Alberta, Canada T6G 2H7

⁶Departamento de Farmacia, Facultad de Química y de Farmacia, Pontificia Universidad Católica de Chile, Av Vicuña Mackenna 4860, Santiago, Chile.

⁷Clinical Development, Sandoz, Inc. (A Novartis Division), Princeton, New Jersey 08540, United States of America.

⁸Drug Product Science and Technology, Bristol-Myers Squibb Company, New Brunswick, New Jersey, 08903-0191.

⁹US Food & Drug Administration (US FDA), Office of Clinical Pharmacology, Office of Translational Sciences, CDER, FDASilver Spring, Maryland, United States of America.

¹⁰Subdepto. Biofarmacia y Equivalencia Terapéutica, Agencia Nacional de Medicamentos (ANAMED), Instituto de Salud Pública de Chile, Santiago, Chile y Facultad de Farmacia, Universidad de Valparaíso, Chile

*Corresponding author:

Bart Hens

Address: Herestraat 49, Box 921, Gasthuisberg, 3000 Leuven, Belgium

Phone: +3216330302

Email: bart.hens@kuleuven.be

31 **Abstract**

32 The gastrointestinal (GI) tract is one of the most popular and used routes of drug product
33 administration due to the convenience for better patient compliance and reduced costs to the patient
34 compared to other routes. However, its complex nature poses a great challenge for formulation scientists
35 when developing more complex dosage forms such as those combining two or more drugs. Fix dosed
36 combination (FDC) products are two or more single active ingredients combined in a single dosage form.
37 This formulation strategy represents a novel formulation which is as safe and effective compared to every
38 mono-product separately. A complex drug product, to be dosed through a complex route, requires judicious
39 considerations for formulation development. Additionally, it represents a challenge from a regulatory
40 perspective at the time of demonstrating bioequivalence (BE) for generic versions of such drug products.
41 This report gives the reader a summary of a two-day short course that took place on the third and fourth of
42 November at the annual association of pharmaceutical scientists (AAPS) meeting in 2018 at Washington,
43 D.C. This manuscript will offer a comprehensive view of the most influential aspects of the GI physiology
44 on the absorption of drugs and current techniques to help understand the fate of orally ingested drug
45 products in the complex environment represented by the GI tract. Through case studies on FDC product
46 development and regulatory issues, this manuscript will provide a great opportunity for readers to explore
47 avenues for successfully developing FDC products and their generic versions.

48 **From Stomach to Large Intestine: A Thorough Review of Gastrointestinal Physiology – Maura**
49 **Corsetti, MD, PhD and Bart Hens, PharmD, PhD**

50 From an anatomical point of view, the stomach is divided into a fundus, corpus (*i.e.*, body) and
51 antrum region, but when it comes to motor function two parts can be distinguished: the proximal stomach,
52 consisting of the fundus and the proximal part of the corpus, and the distal stomach consisting of the distal
53 part of the corpus and the antrum. The motility of the proximal stomach is characterized by a maintained
54 status of contractions of the smooth muscle (tone), whereas the distal stomach generates phasic
55 contractions. During the interdigestive phase, the proximal stomach muscle tone is high, whereas the distal

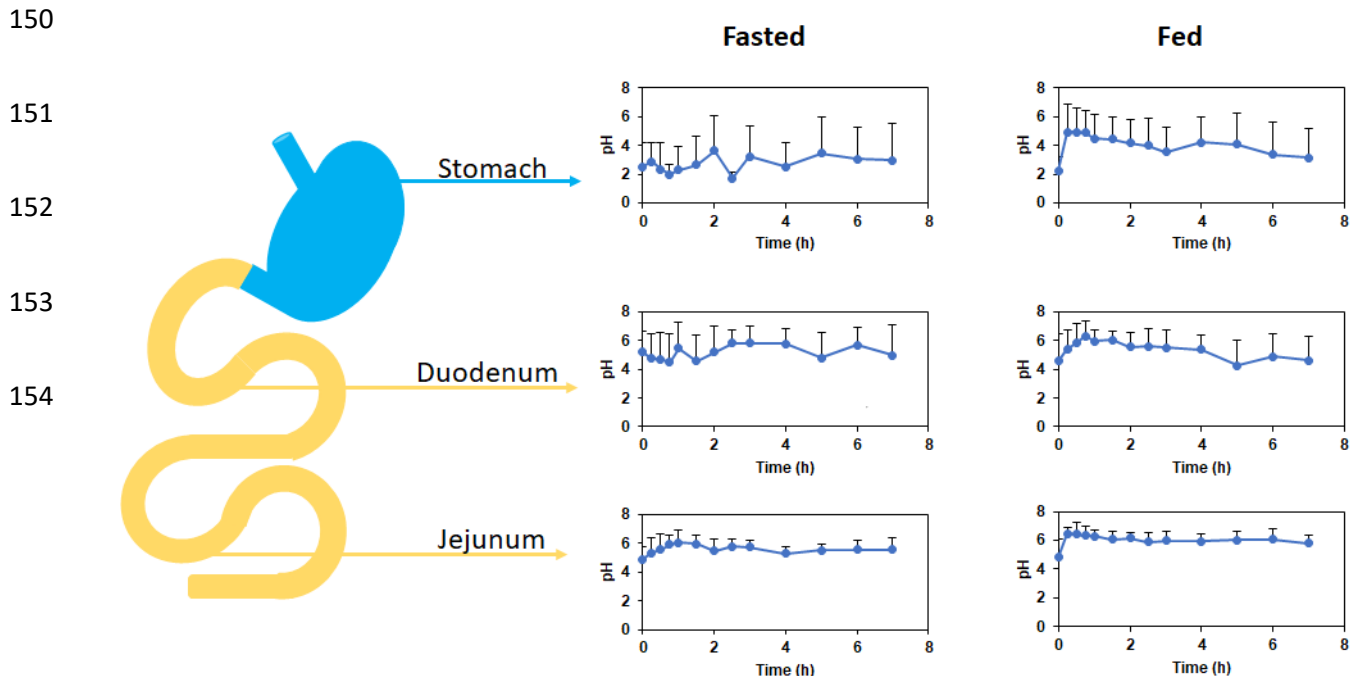
56 stomach is engaged in a recurrent motor pattern known as the migrating motor complex (MMC) [1]. This
57 complex involves the stomach and the majority of the small bowel (but not the distal small bowel) with
58 three phases: phase I, a quiescent phase with no contractions; phase II with until recently considered random
59 contractions; phase III with a sudden onset of repetitive contractions that also ends abruptly. The phase III
60 can start in the stomach or in the proximal small intestine and then migrate towards the distal ileum. Gastric
61 pH fluctuates during the MMC, with the antral pH being lowest (more acidic) just prior to the start of phase
62 III contractions, and higher at the start of phase I. This change in pH is due to an increase in acid and pepsin
63 secretion that accompanies phase III of the MMC, and bile-free, bicarbonate reflux from the duodenum.
64 Intestinal and pancreatic secretions (*e.g.*, water, bicarbonate and pancreatic enzymes) increase during phase
65 III contractions of the small intestine [2,3]. As soon as the food is ingested, the proximal stomach will relax
66 to accommodate the food, followed by a tonic contraction of the proximal stomach which will push the
67 food more distally. The distal stomach will mix and grind the food by powerful and regular contractions.
68 The duodenum is exposed to nutrients almost directly after the ingestion of food and this will activate a
69 multitude of duodeno-gastric negative-feedback mechanisms, as for instance mediated through vagal
70 reflexes and hormonal signals. This will delay the arrival of acidic, hyperosmotic, or calorie-rich gastric
71 contents into the duodenum by inhibiting proximal gastric tone, and phasic contractions, stimulating the
72 closure of the pylorus [4]. The physical consistency, fat content and caloric load of the meal play a relevant
73 role in regulating the motor response of the stomach. Liquids of low caloric density empty under the
74 pressure gradient created by the fundus tone and the little motor action of the distal stomach in an
75 exponential fashion. Digestible food of more solid consistency requires antral trituration until the particle
76 size is reduced [5]. The time that the stomach takes to reduce the particles may explain the lag phase
77 observed before emptying can start. Thus, gastric emptying occurs in two periods: the lag period
78 (responsible for digestion of solid material) and the post-lag, linear emptying period when digested solid
79 particles or liquids can easily be emptied from the stomach. Non-digestible solids are usually emptied from
80 the stomach with the inter-digestive phase III of MMC [5]. A recent study demonstrated the impact of these
81 phase III contractions to clear ibuprofen from the stomach into the small intestine [6]. These contractions

82 in combination with the pH played a pivotal role in the onset of intestinal absorption, determining the
83 plasma C_{max} and T_{max} . A clinical aspiration study was recently performed to investigate the gastric emptying
84 rate of a glass of water in fasted and fed state conditions [7]. A standardized dose of phenol red was added
85 to the glass of water and ingested by healthy subjects. After drinking the glass of water, gastrointestinal
86 (GI) fluids were aspirated from the stomach, duodenum and jejunum. Based on computational modeling,
87 authors identified that gastric emptying of a glass of water is tremendously rapid, especially in fasted state,
88 and will be triggered by the present motility at the time of water administration [7–9]. Scintigraphy is
89 considered the gold standard to study gastric emptying in humans, and this is normally defined by the
90 percentage of gastric retention at 1 h, 2 h and at 4 h. However, the use of a single summary outcome
91 measurement does not allow to capture the above-reported complex mechanisms activated by a meal [10].
92 Nottingham has published the normal values of a gastric emptying test based on a liquid meal, as described
93 by Parker and co-workers, to obtain a comprehensive assessment of gastric motor and sensory function.
94 This test allows differentiating an early and a late phase of gastric emptying for a liquid meal that may
95 reflect the gastric accommodation and the antral component of the gastric emptying [10,11]. Recently, two
96 techniques have been developed to study the gastric function. The SmartPill® is an ingestible device (26
97 mm by 13 mm) measures intraluminal pH, pressure and temperature. It wirelessly transmits data to a
98 wearable external recorder, allowing ambulatory studies at home [12,13]. The variations in luminal pH, as
99 well as the drop in temperature after defecation, allows accurate measurement of regional as well as whole
100 gut transit times. However, it should be noted that in consideration of the dimension of the device does not
101 reflect the gastric emptying of normal digestible food and indeed the gastric emptying has been found to be
102 longer than that measured by scintigraphy [13]. In any case, this technique has the advantage of being non-
103 invasive and of combining the measurement of pH and of the whole gut transit time. Besides telemetric
104 capsules, magnetic resonance imaging (MRI) has been recently applied to the study the GI function and
105 this technique offers some major advantages compared to other techniques: it is non-invasive, does not
106 expose subjects to ionizing radiation, and does not require any contrast medium. It is a unique technique

107 that offers the possibility of simultaneously measuring gastric, small intestinal and colonic volumes, the
108 physicochemical characteristics of the luminal environment, transit rate and to quantify motility [14]. This
109 technique has not yet been standardized across research centers and for the moment does not allow the
110 evaluation of gastric function in an upright position [15]. In summary, the human stomach is more complex
111 as it seems and can play a major role in further intraluminal drug behavior along the intestinal tract where
112 absorption takes place.

113 Beyond the stomach, the intraluminal processes in the small intestine will play a pivotal role with
114 respect to drug absorption. In this second talk, there was a specific focus on (i) the residual intestinal fluid
115 volumes, (ii) the characterization and composition of the intestinal fluids and (iii) the permeability of the
116 intestinal wall for drug compounds. The residual fluid volumes in the intestinal tract are rather scarce and
117 not homogeneously distributed as a pool of water from the proximal towards the distal part. Distribution of
118 these fluids is organized in different fluid pockets [9,16]. The variability in the number of pockets and the
119 actual volume for each pocket is tremendously high between healthy subjects, as highlighted by Mudie and
120 co-workers [9]. This finding was an important investigation for formulation scientists to be aware of the
121 fact that the intestinal tract is not like a ‘swimming pool’, completely filled with water. The prediction of
122 the *in vivo* performance of orally administered drug products has shown to be more accurate when applying
123 the fluid dynamics as observed by Mudie *et al.* instead of using static and high volumes. This was observed
124 for posaconazole, a weakly basic compound, for which the *in vivo* performance was predicted by using a
125 dynamic fluid and pH model in simulation software [17]. Although this model shows to have an impact on
126 predicting the *in vivo* performance for compounds suffering from a poorly aqueous solubility, authors
127 concluded that this model may not have an immense impact on the predicted systemic exposure for
128 compounds characterized by a high solubility. Moreover, as mentioned before, there is huge intersubject
129 variability in the number and volume of pockets. For instance, one subject showed to have only 2 pockets
130 with a total volume of 1.4 mL whereas another subject demonstrated to have 23 pockets with a total volume
131 of 160 mL. A follow-up study aims to unravel a potential link between the appearance of fluid pockets and

132 the present motility [14]. In the seventies, Vantrappen *et al.* observed a higher secretion rate of bicarbonate
 133 shortly after an upper GI phase III contraction [3]. In doing so, the gastric acid of the stomach entering the
 134 small intestine could directly be neutralized by the bicarbonate buffer. This so-called '*secretomotor*
 135 *complex*' is highly likely to be a responsible factor in the formation of water pockets inside the intestinal
 136 tract. Besides gaining knowledge with respect to the present volumes in the GI tract, the composition of
 137 these fluids is another important aspect. In a recent study, human duodenal fluids were aspirated from 20
 138 healthy subjects in the fasted and fed state [18]. The fed state was simulated by ingestion of a liquid meal
 139 (*i.e.*, 400 mL of Ensure Plus®, equal to 700 calories). After aspiration of these fluids as a function of time,
 140 fluids were analyzed for pH and endogenous constituents (bile salts, phospholipids, cholesterol, enzyme
 141 activity and lipid digestion products). The results of this study demonstrated wide variability in the presence
 142 of these constituents from person to person, although the study protocol was the same for each and every
 143 individual [18]. Especially for ionized compounds, the present pH in the intestinal tract is from paramount
 144 importance in order to dissolve and, subsequently, absorb. The research group of Prof. Amidon (University
 145 of Michigan) aspirated GI fluids from 37 healthy subjects after oral intake of an immediate-release
 146 ibuprofen tablet (800 mg) in fasted and fed state conditions [6,19]. Fluids were aspirated from different
 147 segments of the GI tract: stomach, duodenum and jejunum. This study demonstrated the highly fluctuating
 148 pH, especially in the duodenum, which was an important intrinsic factor besides motility explaining
 149 differences in systemic exposure of ibuprofen between and within subjects (Figure 1).



155
156
157
158
159
160

Figure 1: Mean pH versus time profiles in fasting (n = 20) and fed state (n = 17) conditions as measured in the stomach, the duodenum, and the jejunum (mean + SD). Figure depicted from Hens et al. 2017 [6]. Copyright ACS 2017.

161 Besides solubility, absorption has always been a key parameter in estimation of drug performance.
162 Multiple techniques are described in the literature to assess the intestinal permeability of drug compounds.
163 The Loc-I-Gut[®] method, *i.e.*, a double-balloon perfusion system, is an interesting study technique to explore
164 the permeability for drug compounds in the different regions of the GI tract [20,21]. A specific region of
165 the GI tract will be inflated by two balloons and thus separating a specific region of interest. Subsequently,
166 a drug solution will be perfused and the amount of drug that will disappear is a measure for the amount of
167 drug absorbed. The application of this technique has unraveled the intestinal permeability for
168 hydrocortisone in the duodenum, jejunum and ileum. A recent review by Dahlgren *et al.* compiles historical
169 P_{eff} data from 273 individual measurements of 80 substances from 61 studies performed in all parts of the
170 human intestinal tract [22]. This impressive data set has served as a reference for researchers in order to
171 optimize the protocols of *in vitro* setups in order to improve the predictive performance of their in-house
172 absorption tools [23].

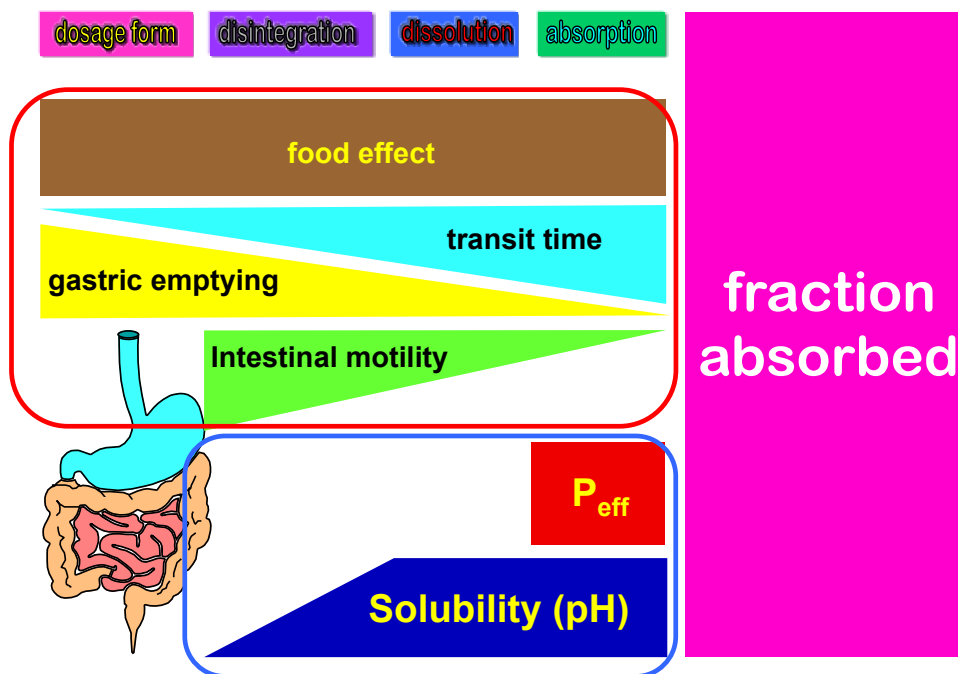
173 With respect to the colonic physiology, recent findings, applying high-resolution manometry
174 (HRM), have demonstrated that colonic motility is mainly represented by non-propagating and retrograde
175 activity and both these activities increased soon after intake of a meal. These colonic motor patterns have
176 the role of delaying the arrival of colonic content to the rectum and of favoring the retrograde filling of the
177 transverse and ascending colon, where the propagating contractions normally start. Propagating
178 contractions, including the high-amplitude propagating contractions associated with movements of solid
179 colon content, represent a minority of the colonic activity and are normally more frequent about 1-2 hours

180 after the meal and upon awakening [24]. The reason of this is likely related to the fact that, in these moments
181 of the day, the arrival of the content accumulated in the distal small bowel during the night and during the
182 inter-digestive periods determine the distension of the ascending and transverse colon that trigger the
183 propagating activity. The prevalence of non-propagating and retrograde activity explains the fact that the
184 normal colonic transit time is slower (about 35 hours) as compared to the small bowel. This allows the
185 colon to perform its functions of absorption, fermentation and to be an adequate reservoir organ. HRM is a
186 useful technique to study colonic motor function but is invasive and normally requires a preparation of the
187 bowel. This makes the technique less attractive when the colonic function needs to be studied under
188 physiological conditions. Recently, other techniques have been applied to study the colonic function. The
189 electromagnetic capsule is an ingestible silicone coated cylindrical magnet (21 mm by 8 mm) used to map
190 the real-time movements of colonic contents. A plate containing a detection matrix of 4 x 4 magnetic field
191 sensors is worn by an ambulatory patient around the abdomen to detect the movements of the pill. This
192 matrix allows mapping of the pill movements in the x-, y-, and z-axis as well as the inclination angles
193 applied by the colon. The pill allows evaluation of the direction (anterograde and retrograde), velocity and
194 length of movement of intraluminal content allowing the calculation of the colonic transit time. Recent
195 studies have also demonstrated the first identification of colonic motor patterns consistent with those seen
196 with HRM [25]. Moreover, MRI has also been introduced as it is able to measure both the colon free water
197 content and the “fluidity” of the colonic content [26]. Recent animal studies have demonstrated that the
198 colon is able to adapt to the physical characteristics of the intraluminal content and develops different motor
199 response according to the presence of more or less fluid content [27]. It is highly likely that these
200 physiological variables play a pivotal role in the dissolution and/or absorption of drugs that are triggered to
201 be released at the colonic site in the human GI tract.

202 **Integration of GI Physiology Into a Predictive Dissolution Device: Where to Start? – Raimar**
203 **Löbenberg, PhD**

204 The GI tract is a complex and not well-understood sequence of organs with changing environments
205 as a function of time. However, an in-depth mechanistic understanding of the obstacles and opportunities
206 in each segment is necessary to achieve optimal drug absorption and bioavailability (BA) (Figure 2).

Oral drug absorption factor



207
208 **Figure 2:** An overview of the different GI physiological variables that can have a major impact on oral drug behavior in the GI tract.

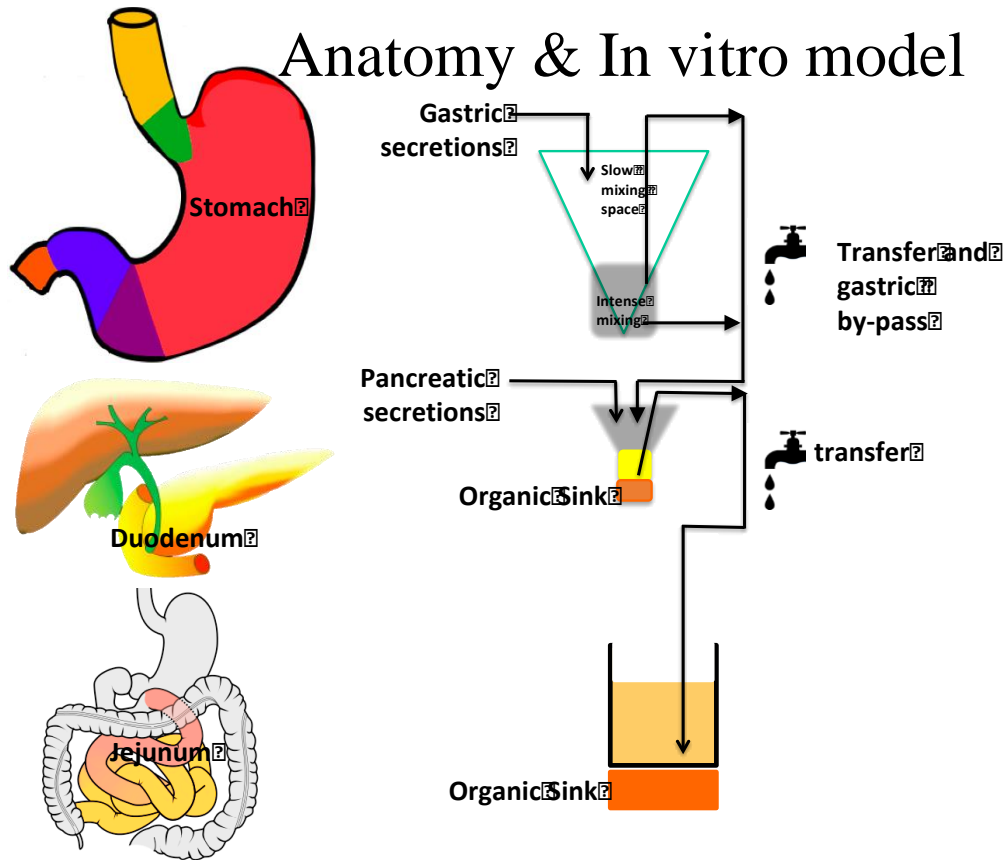
209
210 Figure 2 shows multiple factors impacting the fraction dose absorbed without considering
211 metabolic or drug stability compromising degradation processes. The Biopharmaceutics Classification
212 System (BCS), represented by the blue box, focuses on permeability and solubility [28]. However, drug
213 dissolution and solubility depend on additional physiological factors that are summarized in the red box.
214 Motility effects and gastric emptying are known to have an impact on the performance of a drug product but
215 they are seldom considered in drug development. In contrast, food effects, pH effects and solubilization
216 effects by bile salts were studied intensively in the past decades. However, today, there is still no consensus

217 on a universal dissolution media, which can be used in drug development and for *in vitro* performance
218 testing to capture these effects. Early studies evaluated the solubility of glyburide, a BCS class II drug, in
219 biorelevant media [29]. It was shown that the increased solubility in bile salt media (containing sodium
220 taurocholate and egg-lecithin) was suitable to establish an *in vivo-in vitro* correlation (IVIVC) when
221 computer simulations were applied. A linear regression was established in GastroPlus™. Applying a
222 biorelevant solubility value resulted in a regression coefficient of 0.94 for the reference formulation. The
223 prediction error (%) regarding simulated plasma C_{max} and AUC were 7 and 14% , respectively, when using
224 these biorelevant solubility value as an input in GastroPlus™. Solubility values obtained in aqueous media
225 (pH 6.5) resulted in a 38 and 63% prediction error with respect to plasma C_{max} and AUC. Later on, a dynamic
226 dissolution protocol was developed in biorelevant media (*i.e.*, FaSSIF) which again showed predictive
227 power for establishing an IVIVC [30]. The dynamic dissolution protocol was then applied to a flow-through
228 apparatus for montelukast sodium. Again, the biorelevant media gave the best fit to clinically observed data
229 [31]. These early studies were successful to establish IVIVC without considering other GI factors. In a
230 study by Almukainzi *et al.*, the impact of gastric motility on the pharmacokinetics (PK) of meloxicam was
231 studied [32]. It was observed that two formulations (conventional versus fast dissolving) had a similar PK
232 pattern when administered in a rodent model. However, when the gastric motility was impaired the stomach
233 controlled the drug release and therefore the drug absorption for the conventional dosage form. The PK of
234 the fast dissolving formulation was close to the pattern observed in the healthy state. This study indicated
235 that formulation differences, which are not relevant under healthy conditions, might result in significant
236 differences under disease state. This study showed that the stomach in disease conditions is able to
237 negatively impact PK parameters such as plasma C_{max} and T_{max} . Furthermore, it is well accepted that gastric
238 emptying impacts the PK in fasted versus fed state for many drugs. However, less attention is given to the
239 fact that GI motility impacts C_{max} and T_{max} depending on the dosing time and the MMC phase. This might
240 be due to the fact that the PK models used to quantify and describe the PK behavior of drugs smooth-out
241 individually observed variability in the mean PK profiles. However, if motility and PK are both monitored
242 a relationship between observed plasma levels and intestinal motility are getting more obvious. Another

243 factor for alternations in drug absorption is the composition of the intestinal juices. The buffer system in
244 the GI tract is carbonate-based. In routine pharmaceutical quality control (QC) and development, phosphate
245 buffers play a major role while carbonate buffers are seldom used. The choice of phosphate over bicarbonate
246 seems to impact the *in vivo* performance of enteric-coated dosage forms. Early reports show the failure of
247 enteric-coated products *in vivo* (1964) and are confirmed over several decades until today by *in vivo* studies
248 [33–35]. Also, there is evidence that phosphate and carbonate buffers seem to interact differently with the
249 enteric-coated polymers. It is obvious that a re-evaluation of established *in vitro* testing is important to
250 capture *in vivo* relevant performances to avoid product failure. The next important differences, besides
251 buffer nature, are buffer strengths used in *in vitro* dissolution protocols versus the present buffer strength
252 in the GI tract and the impact of the intestinal absorption on drug dissolution. Biphasic dissolution is known
253 for many years as a surrogate to assess the the *in vivo* performance of a drug formulation [36]. Based on
254 the permeated amount of drug appearing in the organic layer, estimations related to the fraction absorbed
255 can be performed [37]. However, its impact on IVIVC has not yet been fully appreciated. In a recent study,
256 we investigated the dissolution behavior of ibuprofen in pharmacopeial and GI equivalent phosphate buffer
257 strength. The results showed that ibuprofen dissolved fully under the pharmacopeial conditions in less than
258 15 min. However, at low buffer strengths, this process took much longer, and the pH of the media changed
259 significantly due to the acetic nature of ibuprofen. However, if a biphasic dissolution test was performed,
260 the pH recovered over time close to the original value. This again demonstrates how important
261 physiologically adapted *in vitro* testing can be to capture what happens *in vivo*. Only this can ensure that *in*
262 *vitro* methods are predictive of *in vivo* performance. The translation of such methods into QC methods
263 needs to be investigated in the future in more detail. The last aspect deals with the irrelevance of *in vitro*
264 behavior on the drug product performance *in vivo*. An example of such rare case is dextromethorphan [38].
265 This drug is absorbed to over 80% in 2 hours but it takes about 15-20 hours to observe the maximum
266 fraction dose absorbed. A classical IVIVC would correlate fraction dose absorbed versus the dose dissolved.
267 However, in this specific case, the IVIVC would be misleading. The drug dissolves fast in the gut and is
268 completely dissolved within 15 min. As mentioned before, >80% will be absorbed into the enterocytes

269 within 2 hours. The drug undergoes lysosomal trapping after entering the enterocyte. As a weak base, it is
270 highly lipophilic at physiological pH in the cytoplasm. As the drug will migrate through the enterocytes
271 from the apical to the basolateral side, it can pass through the membranes of the lysosomes and it can enter
272 into an aqueous environment with a slightly acidic pH. In this organel, the weak base becomes more
273 hydrophilic and, therefore, will be entrapped in the lysosomes. That is why it takes more time to appear
274 in the blood than it takes time to be absorbed. Such drugs dissolution tests are not useful surrogates for *in*
275 *vivo* performance since the dissolution of the drug product cannot be directly correlated to the plasma levels.
276 It is the biological system and its specific environments and drug partition between the cell compartments,
277 that determine the appearance of the drug in the central compartment and not the drug dissolution. In
278 summary, GI drug absorption is highly impacted by different physiological factors. *In vitro* performance
279 testing should consider and include physiologically-adapted test protocols to identify potential clinical
280 relevant dosage form factors. A BCS sub-classification system, which includes acids, bases and neutral
281 molecules can help to identify potential obstacles for oral drug absorption for these different groups [39].
282 To meet all these standards, a potential *in vitro* apparatus, which can simulate the different GI conditions,
283 is shown in Figure 3.

284



285

286

287 **Figure 3:** Illustrative presentation of an *in vitro* dissolution model taking into account the different physiological barriers of the GI tract that may
 288 have a major impact on drug's dissolution and absorption.

289 **In Vitro Dissolution for a Marketed and Generic FDC Drug Product: Bioequivalent or not? –**
 290 **Marival Bermejo, PhD**

291 Development of Fixed-Dose Drug Combination (FDC) products could be challenging when both
 292 drugs do not belong to the same BCS class *i.e.*, when the limiting factors for their absorption are different.
 293 In the first part of the presentation, the relevance of exploring the biopharmaceutical properties of each drug
 294 in the combination product were discussed in the framework of different classification systems. The BCS
 295 system has evolved from a regulatory conservative classification framework in which the main concern is
 296 to ascertain the non-bioequivalence (non-BE) risk to a development tool which can help on the formulation
 297 strategy selection [40,41]. In order to understand the biopharmaceutical limiting factors for a given drug
 298 the cut-offs and methods for permeability and solubility estimation of BCS are modified in the

299 developability classification system (DCS). The DCS considers a higher available fluid volume (500 mL)
300 in the small intestine and the solubility in human intestinal fluids for solubility classification. The volume
301 of 500 mL is calculated based on the co-administered fluid and present residual fluid along the GI tract
302 [40]. Another relevant addition is the differentiation between solubility-limited and dissolution-limited
303 drugs as the formulation approaches may differ. The selection of the dissolution test to explore the risk of
304 the non-equivalence outcome *in vivo* can be made based on the drug physicochemical characteristics. For
305 that purpose, a sub-classification system from BCS was proposed by Tsume *et al.* [39]. BCS class II drugs
306 were sub-classified in neutral (BCS IIc), weak acids (BCS IIa) and weak bases (BCS IIb). Following these
307 sub-divisions, the suggested dissolution tests to forecast *in vivo* behavior differ from class I and III for
308 which simple dissolution apparatus (as USP II) could suffice and from class II and IV for which a gastric
309 compartment and an absorptive sink should be included in order to increase the *in vivo* predictability. To
310 accommodate that need, several dissolution systems have been proposed in the literature and as example
311 several transfer systems and two-phase or biphasic dissolution systems were described [37,42–47]. In the
312 second part of the lecture, the potential effects of formulation excipients were discussed in as well as
313 experimental preclinical models to study those effects. Excipients can affect membrane permeability and
314 metabolism and GI motility either at gastric emptying level or at intestinal level. In Table 1, some
315 experimental methods with useful references are summarized.

316

317

318

319

320

321

322

Table 1: Overview of potential *in vitro/in situ* methods to apply in order to explore a physiological variable of interest.

Effect	Model	Reference (PMID)
Intestinal permeability	Caco-2; <i>In situ</i> perfusion (Rat –Mouse)	[48–52]
Intestinal metabolism	<i>In situ</i> perfusion in addition to mesenteric vein canulation	[48,53,54]
Gastric emptying	Charcoal suspension Rat; Phenol red + Loperamide; Barium suspension	[55–57]
Intestinal motility	Charcoal suspension Rat	[55]

323

324 For instance, the effect of sodium lauryl sulfate (SLS) on the intestinal permeability of fexofenadine
325 was characterized with Doluisio’s closed-loop perfusion method and further evidenced by *in vivo* BA
326 studies in rats [58,59], while the relevance of gastric emptying changes due to excipients as the reason for
327 a failed bioequivalence study was assessed with a barium sulfate gastric emptying test in rats [60]. Finally,
328 the concept of using BCS as a risk assessment tool of bioequivalence(BE) issues was with the aid of a case
329 study of an FDC development. A valsartan/hydrochlorothiazide generic product failed twice the BE test in
330 each one failing for one of the drugs while succeeding for the other one. The application of a biopredictive
331 dissolution test using the Gastrointestinal Simulator (GIS) was successful in reproducing the *in vivo*
332 outcome as differences in disintegration in the stomach chamber and differences in dissolution rate on the
333 intestinal compartments were the apparent reasons for the *in vivo* failure due to different levels of sorbitol
334 and SLS on the generic formulations. To conclude, BCS and/or DCS classification of drugs in an FDC is a
335 tool to define the absorption limiting factors and the relevant physiological variables affecting BA. For
336 FDC with drugs belonging to different BCS classes a combination *in vitro* dissolution methods and
337 preclinical models is necessary to assess formulation performance.

338 **Challenges and Opportunities to Grant BCS and Dose Strength Based Biowaivers for FDC**
339 **Products – Pablo M. González, PhD**

340 FDC products combine two or more active pharmaceutical ingredients (API) in a finished
341 pharmaceutical dosage form at a fixed ratio of doses [61]. FDC products are approved based on the
342 combination rule that states that each component should contribute to product effectiveness and that the
343 combination should also be safe in a particular patient population [62,63]. Safety and efficacy data can be
344 totally (New Drug Application) or partially (505(b)(2)) original or based on previous reports (Abbreviated
345 New Drug Application) [64]. FDC products offer several advantages over co-administration of the single
346 entity product (SEP) such as greatest patient compliance, increased safety and efficacy, minimized abuse
347 potential, and reduced cost for patients. They also offer opportunities for manufacturers to extend
348 intellectual property and exclusivity along product life-cycle [65]. On the other hand, formulating FDC
349 products impose several challenges related to incompatibility between APIs and incompatible interactions
350 with certain excipients. Some drugs might degrade in presence of another (amiodaquine HCL-artesunate),
351 others might be pharmaceutically incompatible (simvastatin-telmisartan) [66], some drugs could display
352 very different viscoelastic properties (metformin-glibenclamide), and others might interact at the absorptive
353 (*e.g.*, intestinal transporters) or post-absorptive (*e.g.*, metabolic enzymes, renal transporters) level.

354 WHO classifies FDC products into 4 different scenarios regarding regulatory requirements for product
355 registration:

- 356 • Scenario I: The new FDC product has the same APIs and doses as an existing FDC product
- 357 • Scenario II: The new FDC product has same APIs and doses as an established regimen of single
358 entity products (SEP)
- 359 • Scenario III:
 - 360 ○ a) The new FDC product combines APIs with established safety and efficacy data but that
361 have not been used in combination for that particular indication

362 ○ b) The new FDC product comprises a combination of APIs with established safety and
363 efficacy but will be used in a different dosage regimen

364 • Scenario IV: The new FDC product contains one or more new chemical entity (NCE)

365 BE studies are required in order to bridge pivotal clinical data of the reference listed drug (RLD)
366 product(s) to safety and efficacy of FDC products belonging to Scenarios I and II. While the design of BE
367 study for scenario I is standard, in scenario II the *in vivo* performance (*e.g.*, PK end-points) of the FDC
368 product is compared to the co-administration of the SEPs. In both cases, successful BE indicates the absence
369 of (or similar) PK interactions between APIs. However, BE studies for FDC products are challenging due
370 to: i) potential changes in PK intra-subject variability in the combination product; ii) non-linear PK in a line
371 of strengths; iii) drug-formulation interactions; and iv) differential impact of food on API PK when
372 administered as a combination product [67]. These considerations make biowaivers a highly attractive
373 opportunity for manufacturers to fulfill the BE requirement. Currently, WHO, the Food and Drug
374 Administration (FDA), the European Medicines Agency (EMA), the International Conference on
375 Harmonisation (ICH), and Health Canada allow BCS-based biowaivers for immediate release (IR) FDC
376 products containing high-solubility APIs only [68–70]. Thus, FDC products containing BCS class I and/or
377 III APIs could apply for a biowaiver. In general, dissolution, and compositional requirements are the same
378 as those for SEP, with some differences among jurisdictions. For BCS class I API FDA requires the use of
379 excipients present in currently FDA-approved IR products, while EMA encourages the use of similar
380 amounts of the same excipients as the reference product. The 2018 ICH Guidance on BCS-based biowaivers
381 states that critical excipients (*e.g.*, polysorbate 80, sorbitol) must be within $\pm 10\%$ of reference product. On
382 the other hand, there is a consensus among jurisdictions regarding the impact excipients might have on BCS
383 class III drugs, such that agencies require excipients to be qualitatively (Q1) the same and quantitatively
384 (Q2) very similar to the reference product. FDA and ICH guidances contain tables with allowable
385 compositional differences of excipients (by function) relative to the reference product. The implementation
386 of a BCS-based biowaiver for a scenario I-type FDC product is straight forward provided products are

387 pharmaceutically equivalents and dissolution and compositional requirements are fulfilled. Additionally,
388 FDA might accept BCS-based biowaivers for pharmaceutical alternatives if appropriately justified. On the
389 other hand, a BCS-based biowaiver for scenario II-type FDC products impose some challenges for both
390 manufacturers and regulatory agencies. First, different single-entity RLD products might be registered in
391 different regions, implying that a manufacturer would have to perform multiple biowaiver studies if
392 pursuing approval in various jurisdictions. This can be further complicated by the fact that unlike FDA,
393 EMA does not publish a list with RLD for different European countries. Second, FDC containing
394 incompatible APIs need to incorporate a segregation technology (*e.g.*, bilayer tables, tablet-in-tablet, etc.)
395 in order to obtain a stable product. In this case, it might be difficult to account for the compositional
396 requirement between the FDC product and the respective SEP. Third, dissolution methods to study FDC
397 products with large dose disparity between APIs (*i.e.*, dose ratio > 50) might be analytically challenging.
398 This could be further complicated in cases where APIs display divergent pH-dependent stability in the
399 physiological range. Furthermore, RLD SEPs might use different dissolution apparatus (*e.g.*, basket or
400 paddle) such that manufacturer might have to develop and validate two dissolution methods for one FDC
401 product. Fourth, there is a chance for pre-absorptive PK drug-drug or drug-formulation interactions (DFI)
402 in FDC products that could be either different or absent when the SEPs are co-administered. Both FDA and
403 EMA have published guidelines regarding studying drug-drug interactions (DDI) at the transporter level
404 [71,72]. FDA has also published methodological recommendations to study *in vitro* transporter-mediated
405 DDI [71]. While agencies require sponsors to study intestinal efflux transporter-mediated DDI (*i.e.*, P-
406 glycoprotein, breast cancer resistance protein), there is currently no published recommendation on studying
407 potential DDI mediated by intestinal uptake transporters. This seems surprising since it is well recognized
408 that intestinally expressed uptake transporters interact with a vast number of drugs belonging to structurally
409 diverse chemical and therapeutic classes [73]. Moreover, there is growing evidence that pharmaceutical
410 excipients can inhibit both efflux and uptake intestinal transporters *in vitro* and *in situ*. Documented
411 examples include PEG-ylated surfactants, sorbitan fatty acid esters, and polyethylene glycol [74–76]. While
412 there is a consensus that DDI or DFI might be of minor clinical relevance for BCS class I drugs, there also

413 a concern that these interactions could greatly impact the oral absorption of low permeability APIs. FDC
414 products also offer opportunities for developing a line of strengths that can be used to optimize therapy by
415 dose titration. Intermediate and low strengths could apply for a dose strength (DS)-based biowaiver
416 provided there is at least one strength (typically the highest) that successfully demonstrated BE to the
417 reference product *in vivo*. Dose strength-based biowaivers are applicable to APIs that are not eligible for
418 BCS-based biowaivers and to pharmaceutical forms other than IR (*i.e.*, modified-release, delayed-release).
419 Common requirements for DS-based biowaivers among jurisdictions are linear PK in the therapeutic dose
420 range, with a chance for bracketing approach between the highest and the lowest strength, and same
421 manufacturing process for the strength line [77]. The dose range for a FDC will be dependent on the additive
422 or synergistic effect of the investigational drugs. The interaction between the drugs are assessed in drug-
423 drug interaction and PK-PD studies. Subsequently, exposure-response models can be used for Phase 2B
424 dose selection [78]. As in the case of BCS-based biowaivers, DS-based biowaiver requirements are an
425 extension of those for SEPs. Tables 2 and 3 summarize FDA and EMA compositional requirements and
426 dissolution method recommendations for DS-based biowaivers. Data presented in Tables 2 and 3 imply that
427 manufacturers pursuing a DS-based biowaivers in the US and European market might face challenges
428 fulfilling compositional requirements for FDC products based on segregation technologies (*e.g.*, bi-layer
429 tablets) since EMA treats each layer as a separate entity while FDA considers bi-layer tablets as a single
430 unit. Also, in the case of single unit FDC products with large dose disparity between APIs it might be very
431 difficult to fulfill proportionality requirements by both FDA and EMA. More specifically, EMA states that
432 in order to calculate API/excipients proportionality the other API must be considered an excipient.
433 However, it is not clear whether the other API must be considered as a filler for proportionality calculations.
434 Similarly, there is no specific FDA recommendation as to how to consider the other API in bi-layer tables.
435 These discrepancies can hinder simultaneous registration of an FDC product in both USA and Europe.
436 Additionally, while FDA requires bioequivalence studies for the highest dose in the strength line, EMA
437 requires studies at the lowest strength in addition to the highest strength. Finally, the existence of different

438 reference products among jurisdictions increases the number of studies a sponsor needs to execute if seeking
 439 approval in various regions.

440

441 **Table 2:** Comparative compositional requirements to grant dose strength-based biowaivers by FDA and EMA*.

Criteria	FDA	EMA
General composition	All ingredients and APIs are in the same proportion between diff. strengths	Q1 the same and Q2 proportional across different strengths
High-potency APIs	<ul style="list-style-type: none"> • Total weight nearly constant across strengths ($\pm 10\%$ from bio-batch) • Q1 the same across strengths • Only APIs vary across strengths, and one or more excps. 	<ul style="list-style-type: none"> • Amount of API $< 5\%$ core weight or capsule filling • Amount of excps. constant only API varies • Only filler changes to account for changes in APIs
ANDA	Proportion between API and excps. might vary across strengths if same BA is achieved	No special considerations
Bi-layer tablets	Bi-layer tablets are considered as a single unit	Each layer is considered independently
Prolonged Release	<ul style="list-style-type: none"> • Beaded capsules: only number of beads varies across strengths • Single unit products similar general requirements 	<ul style="list-style-type: none"> • Multiple unit formulation: BEq for the highest strength • Single unit formulation: bracketing approach • Release-controlling (or coating) excps. must be the same for the line of strengths.
FDC	Not discussed	<ul style="list-style-type: none"> • Proportionality requirements must be fulfilled for all APIs • The other APIs must be considered an excp., except in bi-layer tablets

442 *Adapted from [77].

443

444

445

446

447

448

Table 3: Dissolution method recommendations by FDA and EMA for dose strength-based biowaivers*.

Criteria	FDA	EMA
IR products	i) Compendial method ii) FDA recommended /USP general chapter iii) Develop new method using diff. agitation speeds, pH (1.2, 4.5, 6.8). Water can be used. Add surfactants if API is poorly soluble	i) pH (1.2, 4.5, 6.8) and QC method ii) If sink condition cannot be achieved at a particular pH for all strengths, compare to dissolution profile of RLD at same dose or using multiple units of lower strengths
MR products	<ul style="list-style-type: none"> • If no compendial method submit ii) + pH (1.2, 4.5, 6.8) for comparisons • Select the most discriminating conditions (agitation, media) based on in vitro and in vivo data 	

450 *Adapted from reference [77].

451

452 **Considering the Biopharmaceutics and Physicochemical Aspects of FDC – Amitava Mitra, PhD**

453 Amitava Mitra, Ph.D. (Sandoz, Inc, A Novartis Division) discussed the key challenges and strategies to
 454 overcome such challenges, in achieving BE for FDC products containing two or more of active ingredients
 455 [67]. The active ingredients of these products may work through different pharmacological pathways and
 456 offer advantages of additive/synergistic effect, reduced dose of each active, and improved patient
 457 compliance. Novel FDCs of Parkinson’s drug, Levodopa, are an example of efforts to improve the clinical
 458 outcome of an old drug using new technologies and mechanisms to improve patient function [79]. However,
 459 combining multiple active ingredients may complicate their individual biopharmaceutic and PK behavior.
 460 The development of controlled or modified release FDC products does add additional challenges due to
 461 changes to the drug release profiles. Such changes in the release profile can change the biopharmaceutic
 462 and pharmacokinetic profiles of the API. Interested readers should review the following published
 463 **references** [67,80–82]. The importance of critically reviewing the physicochemical and biopharmaceutics
 464 properties and their impact on PK of the individual drugs being considered for the FDC was also discussed.
 465 Gaining a thorough understanding of the PK properties of the individual drugs along with the formulation
 466 variables being considered for the FDC is an equally important consideration. Pilot BA studies designed

467 to answer the most pertinent questions relating to the FDC strategy are important and encouraged.
468 However, underpowered studies with too many variables can further confound an already complex issue
469 and should be avoided. Pivotal BE studies should be designed with due consideration of all the
470 physicochemical, biopharmaceutic, and PK data for the compound from all sources. BE study designs
471 specific to highly variable drugs such as scaled BE or cross-over replicate designs may be considered.
472 Leveraging the knowledge gained from varying but synergistic techniques such as *in vitro*
473 solubility/dissolution studies, *in silico* absorption models and IVIVC's, *in vivo* preclinical animal models,
474 and the available *in vivo* clinical data is paramount to the success of the FDC strategy for a given
475 combination. Two case studies were discussed where the use of oral absorption modeling, dissolution data
476 and clinical PK data were used to successfully develop FDC products. In the first case study, the
477 development of a triple combination product was discussed, where one of the active ingredients had a
478 highly variable C_{max} and another active had a long T_{max} due to bile secretion and slow absorption. In this
479 case oral absorption modeling was key to understanding the impact of formulation changes on PK of the
480 three actives and ultimately in development of the FDC product. In the second case study, the development
481 of a double combination product was discussed, where one of the active ingredients was a weak base with
482 high intra-subject CV and steep pH-solubility profile. In this case, data from several relative BA studies
483 and a thorough understanding of the PK and biopharmaceutic properties helped with the successful
484 development of the FDC.

485 **Current Regulatory Requirements to Assess Bioequivalence of FDC Products Worldwide**
486 **(EU/USA/ Latin America/Japan) – Alexis Aceituno, PhD**

487 Although one of the purposes is to combine drugs at fixed dose ratios to simplify treatment of
488 chronic diseases and improve patient adherence, there is a general consensus that this rationale cannot be
489 the only goal behind any development or formulation design [83]. An overview regarding regulations for
490 filing FDC products throughout various jurisdictions around the world shows that progress on this matter
491 has been rather slow. Overall, the development of FDC products by combining previously approved mono-

492 products or starting from the co-formulation of NCEs can follow limited regulatory pathways. Under US
493 regulations the FDCs regulatory fundamentals are described in the Code of Federal Regulations and
494 guidelines that outline the requirements for FDC product approval. The introduction of co-development
495 guidance in 2013 reflects the importance of these pharmaceutical products from a regulatory perspective
496 [62]. The guidances describe that drug product efficacy can rely on BE testing if there is no change in
497 dosing or proposed therapeutic indication for a novel FDC or clinical data are required otherwise. FDC
498 products could follow one of the following regulatory pathways: 505 b(1), 505 b(2) or 505 j covering all
499 the possibilities from new development to generic development. On the other hand, EMA launched several
500 guidelines with respect to the clinical development of FDC products reflecting the proposed therapeutic
501 used and indications of any FDC development [63]. The guidance describes three possible situations with
502 specific requirements for demonstrations of efficacy: 1) the use of an FDC product as add-on treatment if
503 there is a deficient response to one or more drugs to be included in the proposed combination. Drug-Drug
504 (DDI) or PK interaction study may be required if the combination poses a threat with potential clinical
505 consequences; 2) substitution by an FDC product when a reduction of pill burden is sought after.
506 Bioequivalence testing is required and special attention should be paid if the FDC product is dosed at
507 different time intervals, and 3) FDC therapy initiation if the FDC product has not been used previously for
508 any particular indication. Both clinical and pk trial, as well as DDI study, should be performed and
509 submitted prior to approval. In Latin America, there is only one specific guidance for registration of FDC
510 products since 2010 [84]. It describes the definition of FDC products, general consideration for filing and
511 regulatory requirements that depend on the proposed dose scheme or the drugs to be combined. FDC
512 approval can be granted under the following conditions: 1) An FDC product contains the same actives, dose
513 and dose regimes as mono products used concomitantly, therefore the safety and efficacy profiles are well
514 known; to demonstrate efficacy, a bioequivalence study may be sufficient; 2) same conditions as in “1”,
515 but FDC product is going to be used in novel dose or new therapeutic indication and therefore a phase III
516 clinical trial is required; 3) the combination contains one or more new active ingredients and phase I, II and
517 III clinical trials are required to gain approval. In general, there is not a globally applicable guideline for

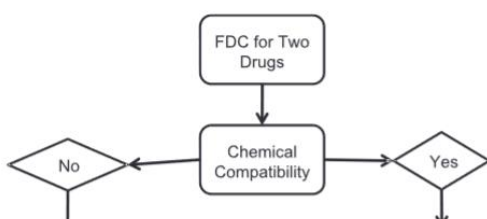
518 FDC product registration, but for specific therapeutic classes and four general cases that are described in a
519 WHO technical report, aiming at guiding pharmaceutical companies for development, approval, and
520 marketing FDC products under less developed jurisdictions [61]. Although generic and hybrid submission
521 pathways seem to be sufficient under most jurisdictions, preclinical and clinical data for novel combinations
522 will always be needed if individual components in FDC products are either known or they are new
523 investigational drugs. However, the idea still persists among regulated entities that different jurisdictions
524 around the world should give more importance to convenience/compliance as a rationale for developing
525 FDC products either containing authorized/new drug entities or authorized drugs only bearing in mind
526 patient's satisfaction or reduced/contained health costs [85]. If generic development is allowed, a BE study
527 design for a FDC product should consider the same principles as if the drugs were given alone, looking for
528 the achievement of equivalence in PK profiles for each FDC active ingredient and their respective either
529 reference FDC or reference mono products. At this point, it is important to realize that PK interactions may
530 have more critical consequences with FDC products than the same drugs given as mono products
531 concomitantly. To conclude, when comparing jurisdictions to obtain FDC product approval, it seems
532 necessary that a balance should be reached between an overcautious registration approach and the potential
533 large public health benefits that would arise from affordable FDC products of proved efficacy. The
534 achievement of broad harmonization in the understanding and application of existent technical guidelines
535 and requirements for FDC product development and registration is still a pending matter.

536 **Formulation Design, Challenges, and Development Considerations for Fixed Dose Combination**
537 **(FDC) of Oral Solid Dosage Forms – Divyakant Desai, PhD**

538 For formulation scientists without prior experience of the FDC development, two decision trees
539 were discussed to select the most suitable formulation development strategy. The first decision tree was
540 related to the formulation design for an FDC product (Figure 4).

541

542



543

544

545

546

547

548 **Figure 4:** Decision tree for the formulation design of a FDC. Figure adopted from Desai and colleagues [86]. Copyright Taylor and Francis

549 2013.

550

551

552

553

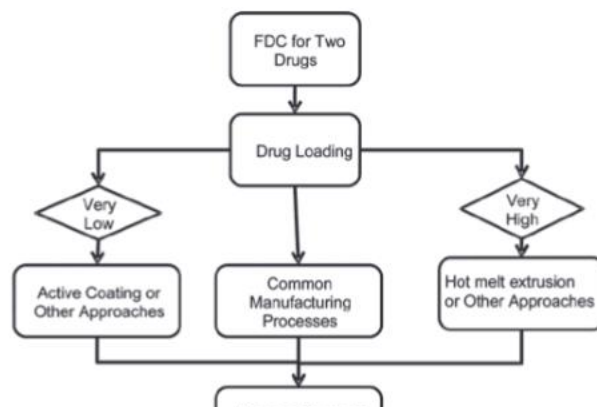
554

555

556 If two drugs are chemically incompatible, multi-layer tablet or a drug-specific multi-particulate
557 system was proposed. If they are compatible, then a monolithic system was proposed unless there is a need
558 to keep them apart in order to maintain the dissolution profiles comparable to the respective single entity
559 product. The second decision tree was about the selection of the manufacturing process for an FDC product
560 (Figure 5).

561

562



563

564

565

566

567

568 **Figure 5:** Decision tree for the manufacturing process selection of a FDC. Figure adopted from Desai and colleagues [86]. Copyright Taylor
569 and Francis 2013.

570

571

572

573

574

575

576 The drug loading in the formulation dictated the selection of the manufacturing process. If the drug
577 loading is high, a hot melt extrusion (HME) or a bi-layer method of manufacturing was proposed. For a
578 formulation with a low drug loading, an active coating approach was proposed. One of the crucial factors
579 in the manufacturing process selection is a pharmaceutical scientist prior experience with the manufacturing
580 process under consideration. A monolithic formulation system, where two drugs are incorporated in a single
581 dose unit, is considered the most simple formulation approach. However, a case study was presented where
582 a second drug, hydrochlorothiazide (HCTZ), was added to the existing formulation of a hypertensive drug
583 [87]. It was shown that povidone (a binder) and poloxamer (a wetting agent) triggered HCTZ degradation

584 under accelerated storage conditions by solubilizing HCTZ in available moisture. Replacement of povidone
585 by Starch 1500, resolved the stability issue and removal of poloxamer did not impact the BE study
586 adversely. For a bi-layer tablet formulation approach, which is normally used to keep two incompatible
587 drugs apart or to maintain two drug release profiles, few critical formulation factors were presented. Those
588 factors include the selection of excipient with high fragmentation tendency such as lactose in the first layer,
589 more deformable material such as microcrystalline cellulose in the second layer, the weight ratio of not
590 more than 1:6 for two layers. It was also emphasized that the tamping force for the first layer should be able
591 to reduce the volume without sacrificing the surface roughness which is essential for the adhesion of the
592 second layer. Two case studies were presented on the bi-layer formulation approach. In the first case study,
593 the compressibility of an extended release metformin formulation was improved by the addition of 1% w/w
594 silicon dioxide. In the second case study, two different grades of fumed silica behaved differently in a bi-
595 layer tablet formulation [88]. Aerosil 200 did not cause layer separation but Aeroperl 300 did. Aeroperl can
596 adsorb relatively large amounts of moisture at any humidity level due to its greater surface area, but it does
597 not retain moisture when the humidity decreases. In contrast, Aerosil adsorbs relatively smaller amounts of
598 moisture but it retains moisture due to its large pore sizes. It was hypothesized that the moisture not retained
599 by Aeroperl could be available for interactions with other layer excipients such crospovidone. The third
600 formulation technique presented was an active coating technology. An active coating can also be used to
601 maintain two separate release profiles and to separate two incompatible drugs. A case study was presented
602 to show how acid and base sensitive molecule was stabilized selecting and minimizing the excipients in a
603 coating material API come in intimate contact with. For example, 1 mg drug is placed with 99 mg of
604 excipients for a 100 mg tablet, the 1 mg drug can react with 99 mg of excipients. However, if 1 mg drug is
605 placed with 9 mg of coating material, the amount of available for a reaction is reduced drastically. It is also
606 a useful technology to make a tablet for a compression sensitive molecule. Although the active coating is
607 useful, it is not as widely used as other technologies because it presents two big challenges. The first
608 challenge is how to detect coating endpoint so that tablets with correct potencies can be manufactured. If a
609 coating process is stopped early, tablets may be sub-potent. On the other hand, if the coating is stopped

610 late, tablets may be super potent. The second challenge is content uniformity (active coat uniformity). The
611 content uniformity can be influenced by various process parameters such as pan load, coating time, number
612 of coating guns, and spray quality. A mathematical model was presented in which model parameters were
613 linked with the process parameters for scale-up. It was shown that the model correctly predicted coating
614 uniformity of tablet weighing 200 mg to 1450 mg in different shapes at a 450 kg commercial scale. In
615 summary, the decision trees are very useful to explore the most suitable formulation and manufacturing
616 process for an FDC formulation. Each formulation approach for an FDC will have its own unique challenges
617 but as illustrated by various case studies, it is possible to overcome these challenges to develop a rugged
618 formulation and a commercially viable manufacturing process using various process analytical technologies
619 (PAT).

620 **Clinical Pharmacology Aspects of Fixed-Dose Combination Drug Development – Dakshina Murthy**
621 **Chilukuri, PhD**

622 Combination products are defined in the Code of Federal Regulations [21 CFR 3.2 (e)] as categories
623 of drug-drug combination products. These products could be two or more approved drugs or investigational
624 drug(s) developed along with an approved drug(s) or two or more investigational drugs developed together.
625 The final products can be FDCs, co-packaged products or separate individual products administered
626 together. Among the reasons why these products are developed are the additive/synergistic effects of drugs
627 for the same disease (*e.g.*, anti-viral and cough/cold drug products). Sometimes when two drugs have
628 complementary mechanisms of action they are developed for the same disease as an FDC product. For
629 instance, combining a beta-lactam with a beta-lactamase inhibitor allows for selective killing of bacteria
630 that would otherwise be resistant to the beta-lactam. There are examples of FDCs where one component is
631 included to reduce the adverse events of the other component (*e.g.* naproxen/esomeprazole delayed-release
632 tablets). Most FDCs are oral but there are examples of inhalational (*e.g.*, tiotropium/olodaterol for Chronic
633 Obstructive Pulmonary Disease, (COPD)) and ophthalmic products (*e.g.*, netarsudil/latanoprost for
634 lowering intraocular pressure). The purpose of this presentation was to provide an overview of the clinical
635 pharmacology considerations in FDC development. FDC development offers interesting challenges to drug

636 developers. If two or more new molecular entities (NMEs) are being developed as an FDC then dose-
637 finding studies of the drugs are generally required to determine the appropriate dose of each drug to be
638 combined. If the FDC product contains drug component(s) not included in an approved combination
639 therapy, then a factorial design clinical efficacy/safety study may be required to demonstrate the
640 contribution of each drug component. Drug administration challenges such as the effect of food on the FDC
641 will generally need to be addressed. This scenario could get more complicated when the various drugs
642 proposed in the FDCs have different requirements for administration under fed and fasted conditions or
643 when the drugs have different dosing frequency. These scenarios generally require a closer look at the FDC
644 formulation and potential for additional BA studies. Dose adjustments of FDCs in specific populations are
645 potentially problematic given the formulation inflexibility. The typical study conducted as part of the
646 development program of an FDC is a relative BA study. The purpose of the BA study of an FDC is to
647 compare the rate and extent of absorption of each active drug ingredient or therapeutic moiety in the FDC
648 to the rate and extent of absorption of each active drug ingredient or therapeutic moiety administered
649 concurrently as separate, single-ingredient preparations [21 CFR 320.25(g)]. Generally, a two-treatment,
650 single-dose, fasting study of the FDC versus single-ingredient drug products at the highest strength of the
651 combination product with matching doses of individual drug products is recommended [89]. Alternative
652 study designs such as a three-treatment study design comparing the combination drug product versus single-
653 ingredient drug products administered separately may be appropriate. A single-dose, food-effect study on
654 the FDC is usually conducted to evaluate the effect of food on the FDC. Case studies related to BA studies
655 conducted to support approval of FDCs were presented along with examples of FDCs approved based on
656 factorial design studies for the FDCs in comparison versus the individual components administered
657 separately. The FDA guidance entitled “*Codevelopment of Two or More New Investigational Drugs for*
658 *Use in Combination*” lays out the scenarios where a factorial design study may be appropriate to establish
659 the contribution of the individual components in the FDC.

660 **Concluding Remarks and Future Perspectives**

661 Market access for FDC products is challenging in terms of achieving bioequivalence to co-
662 administration of the individual mono-products, but also because of formulation challenges (compatibility
663 of API's, doses). However, we should not neglect the impact of GI physiology on oral drug behavior which
664 can result in intersubject differences in systemic outcome, potentially leading to failures in bioequivalence
665 studies. Therefore, it's important to finalize a clear link between formulation strategy and clinical
666 evaluation, supported by guidelines of regulatory authorities. In addition, the contribution of *in vitro*
667 predictive dissolution testing can help assist regulatory decisions with respect to the approval of FDC
668 products in a sense that these models identify the underlying GI variables playing a crucial role in the
669 absorption process inside the GI tract. From an academic point of view, these clinically-relevant dissolution
670 models can be optimized and validated when pharmaceutical companies would share their non-BE
671 formulations (*i.e.*, clinical failures). When they do so, the underlying problems can be unraveled which will
672 be taken into account by formulations scientists when formulating FDC products.

673 **Acknowledgments**

674 Bart Hens is a postdoctoral fellow of the Flemish Research Council (FWO – applicant number:
675 12R2119N).

676 **Disclaimer**

677 This report represents the scientific views of the authors and not necessarily that of the regulatory
678 authorities presented in this manuscript (U.S. Food and Drug Administration and ANAMED).

679

680 **References**

- 681 1. Janssen P, Vanden Berghe P, Verschueren S, Lehmann A, Depoortere I, Tack J. Review article: the role
682 of gastric motility in the control of food intake. *Aliment Pharmacol Ther.* 2011;33:880–94.
- 683 2. Deloose E, Janssen P, Depoortere I, Tack J. The migrating motor complex: control mechanisms and its
684 role in health and disease. *Nat Rev Gastroenterol Hepatol.* 2012;9:271–85.

- 685 3. Vantrappen GR, Peeters TL, Janssens J. The Secretary Component of the Interdigestive Migrating
686 Motor Complex in Man. *Scandinavian Journal of Gastroenterology*. 1979;14:663–7.
- 687 4. Farré R, Tack J. Food and symptom generation in functional gastrointestinal disorders: physiological
688 aspects. *Am J Gastroenterol*. 2013;108:698–706.
- 689 5. Pasricha PJ, Camilleri M, Hasler WL, Parkman HP. White Paper AGA: Gastroparesis: Clinical and
690 Regulatory Insights for Clinical Trials. *Clin Gastroenterol Hepatol*. 2017;15:1184–90.
- 691 6. Hens B, Tsume Y, Bermejo M, Paixao P, Koenigsknecht MJ, Baker JR, et al. Low Buffer Capacity and
692 Alternating Motility along the Human Gastrointestinal Tract: Implications for in Vivo Dissolution and
693 Absorption of Ionizable Drugs. *Mol Pharm*. 2017;14:4281–94.
- 694 7. Paixão P, Bermejo M, Hens B, Tsume Y, Dickens J, Shedden K, et al. Gastric emptying and intestinal
695 appearance of nonabsorbable drugs phenol red and paromomycin in human subjects: A multi-
696 compartment stomach approach. *Eur J Pharm Biopharm*. 2018;129:162–74.
- 697 8. Oberle RL, Chen TS, Lloyd C, Barnett JL, Owyang C, Meyer J, et al. The influence of the interdigestive
698 migrating myoelectric complex on the gastric emptying of liquids. *Gastroenterology*. 1990;99:1275–82.
- 699 9. Mudie DM, Murray K, Hoad CL, Pritchard SE, Garnett MC, Amidon GL, et al. Quantification of
700 gastrointestinal liquid volumes and distribution following a 240 mL dose of water in the fasted state.
701 *Mol Pharm*. 2014;11:3039–47.
- 702 10. Parker HL, Tucker E, Blackshaw E, Hoad CL, Marciani L, Perkins A, et al. Clinical assessment of gastric
703 emptying and sensory function utilizing gamma scintigraphy: Establishment of reference intervals for
704 the liquid and solid components of the Nottingham test meal in healthy subjects. *Neurogastroenterol*
705 *Motil*. 2017;29.
- 706 11. Parker H, Hoad CL, Tucker E, Costigan C, Marciani L, Gowland P, et al. Gastric motor and sensory
707 function in health assessed by magnetic resonance imaging: Establishment of reference intervals for the
708 Nottingham test meal in healthy subjects. *Neurogastroenterol Motil*. 2018;30:e13463.
- 709 12. Cassilly D, Kantor S, Knight LC, Maurer AH, Fisher RS, Semler J, et al. Gastric emptying of a non-
710 digestible solid: assessment with simultaneous SmartPill pH and pressure capsule, antroduodenal
711 manometry, gastric emptying scintigraphy. *Neurogastroenterology & Motility*. 2008;20:311–9.
- 712 13. Diaz Tartera HO, Webb D-L, Al-Saffar AK, Halim MA, Lindberg G, Sangfelt P, et al. Validation of
713 SmartPill® wireless motility capsule for gastrointestinal transit time: Intra-subject variability, software
714 accuracy and comparison with video capsule endoscopy. *Neurogastroenterol Motil*. 2017;29:1–9.
- 715 14. Heissam K, Abrehart N, Hoad CL, Wright J, Menys A, Murray K, et al. Measuring fasted state gastric
716 motility before and after a standard BA/BE 8 oz drink of water: validation of new MRI imaging protocols
717 against concomitant perfused manometry in healthy participants. *Washington D.C.*; 2018.
- 718 15. Hoad C, Clarke C, Marciani L, Graves MJ, Corsetti M. Will MRI of gastrointestinal function parallel the
719 clinical success of cine cardiac MRI? *Br J Radiol*. 2018;20180433.

- 720 16. Schiller C, Fröhlich C-P, Giessmann T, Siegmund W, Mönnikes H, Hosten N, et al. Intestinal fluid
721 volumes and transit of dosage forms as assessed by magnetic resonance imaging. *Aliment Pharmacol*
722 *Ther.* 2005;22:971–9.
- 723 17. Hens B, Bolger MB. Application of a Dynamic Fluid and pH Model to Simulate Intraluminal and
724 Systemic Concentrations of a Weak Base in GastroPlus™. *J Pharm Sci.* 2019;108:305–15.
- 725 18. Riethorst D, Mols R, Duchateau G, Tack J, Brouwers J, Augustijns P. Characterization of Human
726 Duodenal Fluids in Fasted and Fed State Conditions. *J Pharm Sci.* 2016;105:673–81.
- 727 19. Koenigsknecht MJ, Baker JR, Wen B, Frances A, Zhang H, Yu A, et al. In Vivo Dissolution and Systemic
728 Absorption of Immediate Release Ibuprofen in Human Gastrointestinal Tract under Fed and Fasted
729 Conditions. *Mol Pharm.* 2017;14:4295–304.
- 730 20. Dahlgren D, Roos C, Lundqvist A, Abrahamsson B, Tannergren C, Hellström PM, et al. Regional
731 Intestinal Permeability of Three Model Drugs in Human. *Mol Pharm.* 2016;13:3013–21.
- 732 21. Lennernäs H. Human intestinal permeability. *J Pharm Sci.* 1998;87:403–10.
- 733 22. Dahlgren D, Roos C, Sjögren E, Lennernäs H. Direct In Vivo Human Intestinal Permeability (Peff)
734 Determined with Different Clinical Perfusion and Intubation Methods. *J Pharm Sci.* 2015;104:2702–26.
- 735 23. Wuyts B, Riethorst D, Brouwers J, Tack J, Annaert P, Augustijns P. Evaluation of fasted and fed state
736 simulated and human intestinal fluids as solvent system in the Ussing chambers model to explore food
737 effects on intestinal permeability. *Int J Pharm.* 2015;478:736–44.
- 738 24. Corsetti M, Costa M, Bassotti G, Bharucha AE, Borrelli O, Dinning PG. First “translational” consensus
739 on terminology and definition of colonic motility as studied in humans and animals by means of
740 manometric and non-manometric techniques. *Nat Rev.* :in press.
- 741 25. Mark EB, Poulsen JL, Haase A-M, Espersen M, Gregersen T, Schlageter V, et al. Ambulatory
742 assessment of colonic motility using the electromagnetic capsule tracking system. *Neurogastroenterol*
743 *Motil.* 2018;e13451.
- 744 26. Wilkinson-Smith VC, Major G, Ashleigh L, Murray K, Hoad CL, Marciani L, et al. Insights Into the
745 Different Effects of Food on Intestinal Secretion Using Magnetic Resonance Imaging. *JPEN J Parenter*
746 *Enteral Nutr.* 2018;42:1342–8.
- 747 27. Costa M, Wiklendt L, Keightley L, Brookes SJH, Dinning PG, Spencer NJ. New insights into neurogenic
748 cyclic motor activity in the isolated guinea-pig colon. *Neurogastroenterol Motil.* 2017;29:1–13.
- 749 28. Amidon GL, Lennernäs H, Shah VP, Crison JR. A Theoretical Basis for a Biopharmaceutic Drug
750 Classification: The Correlation of in Vitro Drug Product Dissolution and in Vivo Bioavailability. *Pharm Res.*
751 1995;12:413–20.
- 752 29. Wei H, Dalton C, Di Maso M, Kanfer I, Löbenberg R. Physicochemical characterization of five
753 glyburide powders: a BCS based approach to predict oral absorption. *Eur J Pharm Biopharm.*
754 2008;69:1046–56.

- 755 30. Wei H, Löbenberg R. Biorelevant dissolution media as a predictive tool for glyburide a class II drug.
756 Eur J Pharm Sci. 2006;29:45–52.
- 757 31. Okumu A, DiMaso M, Löbenberg R. Dynamic dissolution testing to establish in vitro/in vivo
758 correlations for montelukast sodium, a poorly soluble drug. Pharm Res. 2008;25:2778–85.
- 759 32. Almukainzi M, Jamali F, Aghazadeh-Habashi A, Löbenberg R. Disease specific modeling: Simulation of
760 the pharmacokinetics of meloxicam and ibuprofen in disease state vs. healthy conditions. Eur J Pharm
761 Biopharm. 2016;100:77–84.
- 762 33. Al-Gousous J, Amidon GL, Langguth P. Toward Biopredictive Dissolution for Enteric Coated Dosage
763 Forms. Mol Pharm. 2016;13:1927–36.
- 764 34. Levy G, Hollister LE. FAILURE OF U.S.P. DISINTEGRATION TEST TO ASSESS PHYSIOLOGIC AVAILABILITY
765 OF ENTERIC COATED TABLETS. N Y State J Med. 1964;64:3002–5.
- 766 35. Karkossa F, Klein S. Individualized in vitro and in silico methods for predicting in vivo performance of
767 enteric-coated tablets containing a narrow therapeutic index drug. Eur J Pharm Biopharm. 2018;
- 768 36. Shi Y, Gao P, Gong Y, Ping H. Application of a biphasic test for characterization of in vitro drug release
769 of immediate release formulations of celecoxib and its relevance to in vivo absorption. Mol Pharm.
770 2010;7:1458–65.
- 771 37. Xu H, Vela S, Shi Y, Marroum P, Gao P. In Vitro Characterization of Ritonavir Drug Products and
772 Correlation to Human in Vivo Performance. Mol Pharm. 2017;14:3801–14.
- 773 38. Bolger MB, Macwan JS, Sarfraz M, Almukainzi M, Löbenberg R. The Irrelevance of In Vitro Dissolution
774 in Setting Product Specifications for Drugs Like Dextromethorphan That are Subject to Lysosomal
775 Trapping. J Pharm Sci. 2019;108:268–78.
- 776 39. Tsume Y, Mudie DM, Langguth P, Amidon GE, Amidon GL. The Biopharmaceutics Classification
777 System: subclasses for in vivo predictive dissolution (IPD) methodology and IVIVC. Eur J Pharm Sci.
778 2014;57:152–63.
- 779 40. Butler JM, Dressman JB. The developability classification system: application of biopharmaceutics
780 concepts to formulation development. J Pharm Sci. 2010;99:4940–54.
- 781 41. Rosenberger J, Butler J, Dressman J. A Refined Developability Classification System. J Pharm Sci.
782 2018;107:2020–32.
- 783 42. Kostewicz ES, Abrahamsson B, Brewster M, Brouwers J, Butler J, Carlert S, et al. In vitro models for
784 the prediction of in vivo performance of oral dosage forms. Eur J Pharm Sci. 2014;57:342–66.
- 785 43. Psachoulias D, Vertzoni M, Butler J, Busby D, Symillides M, Dressman J, et al. An in vitro methodology
786 for forecasting luminal concentrations and precipitation of highly permeable lipophilic weak bases in the
787 fasted upper small intestine. Pharm Res. 2012;29:3486–98.

- 788 44. Takeuchi S, Tsume Y, Amidon GE, Amidon GL. Evaluation of a Three Compartment In Vitro
789 Gastrointestinal Simulator Dissolution Apparatus to Predict In Vivo Dissolution. *J Pharm Sci.*
790 2014;103:3416–22.
- 791 45. Klein S, Buchanan NL, Buchanan CM. Miniaturized transfer models to predict the precipitation of
792 poorly soluble weak bases upon entry into the small intestine. *AAPS PharmSciTech.* 2012;13:1230–5.
- 793 46. Takano R, Kataoka M, Yamashita S. Integrating drug permeability with dissolution profile to develop
794 IVIVC. *Biopharm Drug Dispos.* 2012;33:354–65.
- 795 47. Mudie DM, Amidon GL, Amidon GE. Physiological parameters for oral delivery and in vitro testing.
796 *Mol Pharm.* 2010;7:1388–405.
- 797 48. Sjögren E, Abrahamsson B, Augustijns P, Becker D, Bolger MB, Brewster M, et al. In vivo methods for
798 drug absorption - comparative physiologies, model selection, correlations with in vitro methods (IVIVC),
799 and applications for formulation/API/excipient characterization including food effects. *Eur J Pharm Sci.*
800 2014;57:99–151.
- 801 49. Rege BD, Yu LX, Hussain AS, Polli JE. Effect of common excipients on Caco-2 transport of low-
802 permeability drugs. *J Pharm Sci.* 2001;90:1776–86.
- 803 50. Rege BD, Kao JPY, Polli JE. Effects of nonionic surfactants on membrane transporters in Caco-2 cell
804 monolayers. *Eur J Pharm Sci.* 2002;16:237–46.
- 805 51. Bermejo MV, Pérez-Varona AT, Segura-Bono MJ, Martín-Villodre A, Plá-Delfina JM, Garrigues TM.
806 Compared effects of synthetic and natural bile acid surfactants on xenobiotic absorption I. Studies with
807 polysorbate and taurocholate in rat colon. *International Journal of Pharmaceutics.* 1991;69:221–31.
- 808 52. Carmona-Ibáñez G, Bermejo-Sanz M del V, Rius-Alarcó F, Martín-Villodre A. Experimental Studies on
809 the Influence of Surfactants on Intestinal Absorption of Drugs Cefadroxil as model drug and sodium
810 taurocholate as natural model Surfactant: studies in rat colon and in rat duodenum.
811 *Arzneimittelforschung.* 1999;49:44–50.
- 812 53. Brouwers J, Mols R, Annaert P, Augustijns P. Validation of a differential in situ perfusion method with
813 mesenteric blood sampling in rats for intestinal drug interaction profiling. *Biopharm Drug Dispos.*
814 2010;31:278–85.
- 815 54. Mols R, Brouwers J, Schinkel AH, Annaert P, Augustijns P. Intestinal perfusion with mesenteric blood
816 sampling in wild-type and knockout mice: evaluation of a novel tool in biopharmaceutical drug profiling.
817 *Drug Metab Dispos.* 2009;37:1334–7.
- 818 55. Guillaume P, Provost D, Lacroix P. Gastrointestinal models: intestinal transit, gastric emptying, and
819 ulcerogenic activity in the rat. *Curr Protoc Pharmacol.* 2008;Chapter 5:Unit5.3.
- 820 56. Goineau S, Guillaume P, Castagné V. Comparison of the effects of clonidine, loperamide and
821 metoclopramide in two models of gastric emptying in the rat. *Fundam Clin Pharmacol.* 2015;29:86–94.
- 822 57. Pestel S, Martin H-J, Maier G-M, Guth B. Effect of commonly used vehicles on gastrointestinal, renal,
823 and liver function in rats. *J Pharmacol Toxicol Methods.* 2006;54:200–14.

- 824 58. Gundogdu E, Mangas-Sanjuan V, Gonzalez-Alvarez I, Bermejo M, Karasulu E. In vitro-in situ
825 permeability and dissolution of fexofenadine with kinetic modeling in the presence of sodium dodecyl
826 sulfate. *Eur J Drug Metab Pharmacokinet.* 2012;37:65–75.
- 827 59. Gundogdu E, Alvarez IG, Karasulu E. Improvement of effect of water-in-oil microemulsion as an oral
828 delivery system for fexofenadine: in vitro and in vivo studies. *Int J Nanomedicine.* 2011;6:1631–40.
- 829 60. Colón-Useche S, González-Álvarez I, Mangas-Sanjuan V, González-Álvarez M, Pastoriza P, Molina-
830 Martínez I, et al. Investigating the Discriminatory Power of BCS-Biowaiver in Vitro Methodology to
831 Detect Bioavailability Differences between Immediate Release Products Containing a Class I Drug. *Mol*
832 *Pharm.* 2015;12:3167–74.
- 833 61. World Health Organization. WHO Expert Committee on Specifications for Pharmaceutical
834 Preparations. *World Health Organ Tech Rep Ser.* 2005;929:1–142, backcover.
- 835 62. US Food & Drug Administration. Guidance for Industry on Fixed Dose Combinations, Co-Packaged
836 Drug Products, and Single-Entity Versions of Previously Approved Antiretrovirals for the Treatment of
837 HIV; Availability [Internet]. *Federal Register.* 2006 [cited 2019 Jan 15]. Available from:
838 [https://www.federalregister.gov/documents/2006/10/18/E6-17324/guidance-for-industry-on-fixed-](https://www.federalregister.gov/documents/2006/10/18/E6-17324/guidance-for-industry-on-fixed-dose-combinations-co-packaged-drug-products-and-single-entity)
839 [dose-combinations-co-packaged-drug-products-and-single-entity](https://www.federalregister.gov/documents/2006/10/18/E6-17324/guidance-for-industry-on-fixed-dose-combinations-co-packaged-drug-products-and-single-entity)
- 840 63. European Medicines Agency. Guideline on clinical development of fixed combination medicinal
841 products. 2017;12.
- 842 64. When to Submit an ANDA vs. a 505(b)(2) Application: FDA Discusses in Draft Guidance [Internet].
843 [cited 2019 Jan 15]. Available from: [https://www.raps.org/regulatory-focus™/news-](https://www.raps.org/regulatory-focus™/news-articles/2017/10/when-to-submit-an-anda-vs-a-505(b)(2)-application-fda-discusses-in-draft-guidance)
844 [articles/2017/10/when-to-submit-an-anda-vs-a-505\(b\)\(2\)-application-fda-discusses-in-draft-guidance](https://www.raps.org/regulatory-focus™/news-articles/2017/10/when-to-submit-an-anda-vs-a-505(b)(2)-application-fda-discusses-in-draft-guidance)
- 845 65. Podolsky SH, Greene JA. Combination drugs--hype, harm, and hope. *N Engl J Med.* 2011;365:488–91.
- 846 66. Kohlrausch A. Bilayer tablet of telmisartan and simvastatin [Internet]. 2006 [cited 2019 Jan 15].
847 Available from: <https://patents.google.com/patent/US20060078615A1/en>
- 848 67. Mitra A, Wu Y. Challenges and opportunities in achieving bioequivalence for fixed-dose combination
849 products. *AAPS J.* 2012;14:646–55.
- 850 68. Food & Drug Administration. Waiver of In Vivo Bioavailability and Bioequivalence Studies for
851 Immediate-Release Solid Oral Dosage Forms Based on a Biopharmaceutics Classification System
852 Guidance for Industry [Internet]. 2015 [cited 2017 Jan 17]. Available from:
853 <http://www.fda.gov/downloads/Drugs/Guidances/ucm070246.pdf>
- 854 69. European Medicines Agency. Guideline on the investigation of bioequivalence [Internet]. 2010.
855 Available from:
856 [http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2010/01/WC50007003](http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2010/01/WC500070039.pdf)
857 [9.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2010/01/WC500070039.pdf)
- 858 70. Canada H, Canada H. Guidance Document: Biopharmaceutics Classification System Based Biowaiver
859 [Internet]. *aem.* 2014 [cited 2019 Jan 15]. Available from: <https://www.canada.ca/en/health->

860 canada/services/drugs-health-products/drug-products/applications-submissions/guidance-
861 documents/biopharmaceutics-classification-system-based-biowaiver.html

862 71. US Food & Drug Administration. In Vitro Metabolism- and Transporter-Mediated Drug-Drug
863 Interaction Studies, and Clinical Drug Interaction Studies-Study Design, Data Analysis, and Clinical
864 Implications; Draft Guidances for Industry; Availability [Internet]. Federal Register. 2017 [cited 2019 Jan
865 15]. Available from: [https://www.federalregister.gov/documents/2017/10/25/2017-23102/in-vitro-](https://www.federalregister.gov/documents/2017/10/25/2017-23102/in-vitro-metabolism--and-transporter-mediated-drug-drug-interaction-studies-and-clinical-drug)
866 [metabolism--and-transporter-mediated-drug-drug-interaction-studies-and-clinical-drug](https://www.federalregister.gov/documents/2017/10/25/2017-23102/in-vitro-metabolism--and-transporter-mediated-drug-drug-interaction-studies-and-clinical-drug)

867 72. European Medicines Agency. European Medicines Agency updates guideline on drug interactions
868 [Internet]. 2012 [cited 2019 Jan 15]. Available from: [https://www.ema.europa.eu/en/news/european-](https://www.ema.europa.eu/en/news/european-medicines-agency-updates-guideline-drug-interactions)
869 [medicines-agency-updates-guideline-drug-interactions](https://www.ema.europa.eu/en/news/european-medicines-agency-updates-guideline-drug-interactions)

870 73. Dobson PD, Kell DB. Carrier-mediated cellular uptake of pharmaceutical drugs: an exception or the
871 rule? *Nat Rev Drug Discov.* 2008;7:205–20.

872 74. Dahlgren D, Roos C, Lundqvist A, Tannergren C, Langguth P, Sjöblom M, et al. Preclinical Effect of
873 Absorption Modifying Excipients on Rat Intestinal Transport of Model Compounds and the Mucosal
874 Barrier Marker 51Cr-EDTA. *Mol Pharm.* 2017;14:4243–51.

875 75. Engel A, Oswald S, Siegmund W, Keiser M. Pharmaceutical excipients influence the function of
876 human uptake transporting proteins. *Mol Pharm.* 2012;9:2577–81.

877 76. Otter M, Oswald S, Siegmund W, Keiser M. Effects of frequently used pharmaceutical excipients on
878 the organic cation transporters 1-3 and peptide transporters 1/2 stably expressed in MDCKII cells. *Eur J*
879 *Pharm Biopharm.* 2017;112:187–95.

880 77. Cardot J-M, Garcia-Arieta A, Paixao P, Tasevska I, Davit B. Implementing the additional strength
881 biowaiver for generics: EMA recommended approaches and challenges for a US-FDA submission. *Eur J*
882 *Pharm Sci.* 2018;111:399–408.

883 78. Maltais F, Hamilton A, Voß F, Maleki-Yazdi MR. Dose Determination for a Fixed-Dose Drug
884 Combination: A Phase II Randomized Controlled Trial for Tiotropium/Olodaterol Versus Tiotropium in
885 Patients with COPD. *Adv Ther.* 2019;36:962–8.

886 79. Silver DE. Clinical experience with the novel levodopa formulation entacapone + levodopa +
887 carbidopa (Stalevo). *Expert Rev Neurother.* 2004;4:589–99.

888 80. Dey S, Chattopadhyay S, Mazumder B. Formulation and Evaluation of Fixed-Dose Combination of
889 Bilayer Gastroretentive Matrix Tablet Containing Atorvastatin as Fast-Release and Atenolol as Sustained-
890 Release. *Biomed Res Int* [Internet]. 2014 [cited 2019 Apr 25];2014. Available from:
891 <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3909979/>

892 81. Riekes MK, Engelen A, Appeltans B, Rombaut P, Stulzer HK, Van den Mooter G. New Perspectives for
893 Fixed Dose Combinations of Poorly Water-Soluble Compounds: a Case Study with Ezetimibe and
894 Lovastatin. *Pharm Res.* 2016;33:1259–75.

895 82. Oh J-H, Lee JE, Kim YJ, Oh T-O, Han S, Jeon EK, et al. Designing of the fixed-dose gastroretentive
896 bilayer tablet for sustained release of metformin and immediate release of atorvastatin. *Drug*
897 *Development and Industrial Pharmacy*. 2016;42:340–9.

898 83. Sleight P, Pouleur H, Zannad F. Benefits, challenges, and registerability of the polypill. *Eur Heart J*.
899 2006;27:1651–6.

900 84. Guia para Registro de Novas Associações em Dose Fixa - Busca - Anvisa [Internet]. [cited 2019 Jan
901 15]. Available from: [http://portal.anvisa.gov.br/resultado-de-](http://portal.anvisa.gov.br/resultado-de-busca?p_p_id=101&p_p_lifecycle=0&p_p_state=maximized&p_p_mode=view&p_p_col_id=column-1&p_p_col_count=1&_101_struts_action=%2Fasset_publisher%2Fview_content&_101_assetEntryId=352621&_101_type=document)
902 [busca?p_p_id=101&p_p_lifecycle=0&p_p_state=maximized&p_p_mode=view&p_p_col_id=column-](http://portal.anvisa.gov.br/resultado-de-busca?p_p_id=101&p_p_lifecycle=0&p_p_state=maximized&p_p_mode=view&p_p_col_id=column-1&p_p_col_count=1&_101_struts_action=%2Fasset_publisher%2Fview_content&_101_assetEntryId=352621&_101_type=document)
903 [1&p_p_col_count=1&_101_struts_action=%2Fasset_publisher%2Fview_content&_101_assetEntryId=35](http://portal.anvisa.gov.br/resultado-de-busca?p_p_id=101&p_p_lifecycle=0&p_p_state=maximized&p_p_mode=view&p_p_col_id=column-1&p_p_col_count=1&_101_struts_action=%2Fasset_publisher%2Fview_content&_101_assetEntryId=352621&_101_type=document)
904 [2621&_101_type=document](http://portal.anvisa.gov.br/resultado-de-busca?p_p_id=101&p_p_lifecycle=0&p_p_state=maximized&p_p_mode=view&p_p_col_id=column-1&p_p_col_count=1&_101_struts_action=%2Fasset_publisher%2Fview_content&_101_assetEntryId=352621&_101_type=document)

905 85. Gautam Y, Bjerrum OJ, Schmiegelow M. The Wider Use of Fixed-Dose Combinations Emphasizes the
906 Need for a Global Approach to Regulatory Guideline Development. *Drug Inf J*. 2015;49:197–204.

907 86. Desai D, Wang J, Wen H, Li X, Timmins P. Formulation design, challenges, and development
908 considerations for fixed dose combination (FDC) of oral solid dosage forms. *Pharm Dev Technol*.
909 2013;18:1265–76.

910 87. Desai D, Rinaldi F, Kothari S, Paruchuri S, Li D, Lai M, et al. Effect of hydroxypropyl cellulose (HPC) on
911 dissolution rate of hydrochlorothiazide tablets. *Int J Pharm*. 2006;308:40–5.

912 88. Narang AS, Rao VM, Desai DS. Effect of antioxidants and silicates on peroxides in povidone. *J Pharm*
913 *Sci*. 2012;101:127–39.

914 89. US Food & Drug Administration. Guidance, Compliance, & Regulatory Information [Internet]. [cited
915 2019 Mar 5]. Available from:
916 <https://www.fda.gov/drugs/guidancecomplianceregulatoryinformation/default.htm>

917

918