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Editorial

Regional Intestinal Drug Absorption: Biopharmaceutics and Drug Formulation

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Abstract: The gastrointestinal tract (GIT) can be broadly divided into several regions: the stomach, the small intestine (which is subdivided to duodenum, jejunum, and ileum), and the colon. The conditions and environment in each of these segments, and even within the segment, are dependent on many factors, e.g., the surrounding pH, fluid composition, transporters expression, metabolic enzymes activity, tight junction resistance, different morphology along the GIT, variable intestinal mucosal cell differentiation, changes in drug concentration (in cases of carrier-mediated transport), thickness and types of mucus, and resident microflora. Each of these variables, alone or in combination with others, can fundamentally alter the solubility/dissolution, the intestinal permeability, and the overall absorption of various drugs. This is the underlying mechanistic basis of regional-dependent intestinal drug absorption, which has led to many attempts to deliver drugs to specific regions throughout the GIT, aiming to optimize drug absorption, bioavailability, pharmacokinetics, and/or pharmacodynamics. In this Editorial we provide an overview of the Special Issue "Regional Intestinal Drug Absorption: Biopharmaceutics and Drug Formulation". The objective of this Special Issue is to highlight the current progress and to provide an overview of the latest developments in the field of regional-dependent intestinal drug absorption and delivery, as well as pointing out the unmet needs of the field.

Keywords: biopharmaceutics; drug absorption; drug solubility/dissolution; intestinal permeability; oral drug delivery; regional/segmental-dependent permeability and absorption

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Oral administration is without a doubt the most preferred and convenient way of drug delivery. Oral drug products are easy to use and usually do not require hospitalization or the assistance of medical staff. Oral intake of drugs may also prevent both the local side effects and the risk of systemic infections associated with injections. However, orally taken drugs must enter the enterocytes and cross through the gastrointestinal tract (GIT) membrane in order to reach the systemic circulation and exert their pharmacological effect. The GIT membrane acts as a barrier against the absorption of xenobiotics, and while some drugs easily overcome this barrier, many other drugs fail to penetrate through this membrane and have to be administered parenterally. These drugs include antibodies, protein/peptides, hormones, and even small molecules. Orally swallowed drugs are very much influenced by the physiological/biochemical conditions throughout the GIT, which may dictate their absorption potential, resulting in significant diversions from the predicted/desired pharmacokinetics and pharmacodynamics.

The GIT can be broadly divided to several regions: the stomach, the small intestine (which is subdivided into the duodenum, jejunum, and ileum), and the colon. The conditions and environment in each of these segments, and even within the segment, are dependent on many factors, e.g., the surrounding pH [1–6], fluid composition [7–9],

transporters expression [10–12], metabolic enzymes activity [13,14], tight junction resistance [15,16], different morphology along the GIT [17,18], variable intestinal mucosal cell differentiation [19,20], changes in drug concentration (in cases of carrier-mediated transport), thickness and types of mucus [21], and resident microflora [22–24]. Each of these variables, alone or in combination with others, can fundamentally alter the solubility/dissolution, the intestinal permeability, and the overall absorption of various drugs [25–28]. This is the underlying mechanistic basis of regional-dependent intestinal drug absorption, which has led to many attempts to deliver drugs to specific regions throughout the GIT, aiming to optimize drug absorption, bioavailability, pharmacokinetics and/or pharmacodynamics.

The objective of this Special Issue is to highlight the current progress and to provide an overview of the latest developments in the field of regional-dependent intestinal drug absorption and delivery, as well as pointing out the unmet needs of the field.

Nowadays, the "3R's Principle", that is, replacement, reduction, and refinement, has greatly influenced scientific research in oral drug development, and several preclinical models have been developed to predict intestinal absorption process, aiming to reduce or even replace human/animal experiments. These methods are thoroughly evaluated in this Special Issue. The differences in anatomical and physiological features along the GIT complicate absorption predictions. Rezende's group demonstrated that the BAMPA (biomimetic artificial membrane permeability assay) over Franz cell apparatus showed acceptable log-linear correlation (R^2 = 0.664) with fraction of dose absorbed in humans (F_a%), as seen for P_{app} in Caco-2 cells (R^2 = 0.805), and, thus, both methods are acceptable for BCS classification [29]. Caco-2 cell predictability has been widely studied, and several authors demonstrated the correlation between Caco-2 cells and structure–activity of the drug [30–32]. In this issue, Huong Ta et al. developed a QSAR model (quantitative structure–activity relationship) using a machine learning-based hierarchical support vector regression (HSVR) scheme [33]. This tool allowed for the development of a model to predict Papp in Caco-2 cells permeability for drugs that are transported across the intestinal membrane not only in passive diffusion but also in transporter-mediated active transport. The group of Bermejo and González-Álvarez demonstrated that in vitro permeability studies in Caco-2 can be used to compare formulation performance and even to explain bioequivalence failures associated with excipient effect on the intestinal membrane [34]. In this study, Ruiz-Picazo et al. showed that permeability differences in rat vs. Caco-2 cells of pravastatin formulations (a BCS class III compound) can explain the bioequivalence failure and the higher C_{max} due to excipient effects on the intestinal membrane in the nonequivalent formulation. In the same article, the authors demonstrated non-similar dissolution profiles with USP apparatus and the relevance of using 500 mL instead of 900 mL [34]. A great research effort is focused on the development of new dissolution systems, mono- and multi-compartmental dynamics models. The adequate in vitro model should be chosen depending on the BCS classification of the studied drug and its physicochemical properties. These in vitro systems combine dissolution and absorption processes and simulate pH or peristaltic changes in luminal conditions; therefore, a mechanistic, physiologically based biopharmaceutics modeling (PBBM) approach to assess the in vivo performance of orally administered drug products (IVIVC) should be used to model the obtained data. These models are more complicated and require adequate software but generate better correlations between in vitro and in vivo values, as demonstrated by Bermejo at al. in their study of different ibuprofen formulations [35]. Several absorption models can be tested with different software, such as Phoenix WinNonlin® [35] or the GastroPlus™ simulator, as was demonstrated by Dahan's group [36], studying the rather complicated intestinal permeability of the BCS class IV drug furosemide that shows high dependency on many biochemical/physiological variables. Another common piece of software in the population pharmacokinetic area is NONMEM, which can be used in modelling absorption due to the flexibility of using custom-made empirical, semi-mechanistic, or physiological-based absorption approaches. Transit compartment models, absorption with and without

lag time, or passive/active absorption kinetics models can be applied. In this context, Ruiz-Garcia et al. modeled dacomitinib absorption differences in the presence/absence of a proton pump inhibitor by comparing several physiologically based absorption models [37].

The behavior of controlled release formulations and the difficulties in predicting the human situation are studied in this Special Issue. Lennernäs et al. thoroughly discuss the predictive ability of rat colon studies in relation to human data and conclude that improved predictability is needed for controlled release formulations, and the use of permeation enhancers to increase colonic permeability could have higher risks than potential rewards [38]. Langguth's group studied the relevance of dissolution and disintegration of controlled release (CR) dosage forms, obtaining good correlations between the two processes [39]. This work may have significant regulatory impact, as it opens the way to extend the dissolution-based waiver concept beyond immediate-release dosage forms. However, the authors conclude that the extrapolation of these results to the in vivo situation should be done with caution due to additional factors that should be considered, e.g., transporter saturation effects, interplay with food and gastric emptying effects, and different hydrodynamics or mechanical stresses; these factors may complicate the correlation between disintegration and bioavailability [39]. Dahan's group investigated the role of segmental-dependent intestinal absorption in controlled release (CR) drug product development. The studied drug was carvedilol due to its zwitterionic nature; thus, this compound changes solubility in different conditions throughout the GIT [40]. The solubility, permeability, and dissolution of the drug were investigated in silico, in vitro, and in vivo, focusing on location-dependent effects. The authors demonstrated that a CR product could modify the drug solubility behavior from class II to I; these results are highly relevant in the decision-making process regarding the development of new CR drug products. The increased interest in drug delivery to the last segments of the GIT has led to new insights in the design of colonic delivery devices; Christfort et al. studied cylindrical, triangular, and cubic microcontainers with amoxicillin and showed that shape and surface texture of microcontainers influence the ex vivo mucoadhesion (cubic microcontainers are more adhered to intestinal mucus than cylindrical microcontainers), and the absorption of amoxicillin was higher from cubic microcontainers than from cylindrical or triangular microcontainers [41].

This Special Issue also includes two highly relevant review articles: the group of K. Sandy Pang focus on intestinal and liver metabolism and drug–drug interactions [42], and Tongzhi et al. focus on regional gut stimulation, concluding that the region of the gut exposed to intraluminal stimuli is of major relevance to the secretion profile of gastrointestinal hormones and associated metabolic responses [43].

Conflicts of Interest: The authors declare no conflict of interest.

References

1. Dahan, A.; Miller, J.M.; Hilfinger, J.M.; Yamashita, S.; Yu, L.X.; Lennernäs, H.; Amidon, G.L. High-Permeability Criterion for BCS Classification: Segmental/pH Dependent Permeability Considerations. *Mol. Pharm.* **2010**, *7*, 1827–1834. [CrossRef]
2. Fairstein, M.; Swissa, R.; Dahan, A. Regional-Dependent Intestinal Permeability and BCS Classification: Elucidation of pH-Related Complexity in Rats Using Pseudoephedrine. *AAPS J.* **2013**, *15*, 589–597. [CrossRef]
3. Kataoka, M.; Fukahori, M.; Ikemura, A.; Kubota, A.; Higashino, H.; Sakuma, S.; Yamashita, S. Effects of gastric pH on oral drug absorption: In vitro assessment using a dissolution/permeation system reflecting the gastric dissolution process. *Eur. J. Pharm. Biopharm.* **2016**, *101*, 103–111. [CrossRef]
4. Zur, M.; Cohen, N.; Agbaria, R.; Dahan, A. The biopharmaceutics of successful controlled release drug product: Segmental-dependent permeability of glipizide vs. metoprolol throughout the intestinal tract. *Int. J. Pharm.* **2015**, *489*, 304–310. [CrossRef] [PubMed]
5. Zur, M.; Gasparini, M.; Wolk, O.; Amidon, G.L.; Dahan, A. The Low/High BCS Permeability Class Boundary: Physicochemical Comparison of Metoprolol and Labetalol. *Mol. Pharm.* **2014**, *11*, 1707–1714. [CrossRef]
6. Zur, M.; Hanson, A.S.; Dahan, A. The complexity of intestinal permeability: Assigning the correct BCS classification through careful data interpretation. *Eur. J. Pharm. Sci.* **2014**, *61*, 11–17. [CrossRef] [PubMed]
7. Figueroa-Campos, A.; Sánchez-Dengra, B.; Merino, V.; Dahan, A.; González-Álvarez, I.; García-Arieta, A.; González-Álvarez, M.; Bermejo, M. Candesartan Cilexetil In Vitro–In Vivo Correlation: Predictive Dissolution as a Development Tool. *Pharmaceutics* **2020**, *12*, 633. [CrossRef]

8. Kostewicz, E.S.; Aarons, L.; Bergstrand, M.; Bolger, M.B.; Galetin, A.; Hatley, O.; Jamei, M.; Lloyd, R.; Pepin, X.; Rostami-Hodjegan, A.; et al. PBPK models for the prediction of in vivo performance of oral dosage forms. *Eur. J. Pharm. Sci.* **2014**, *57*, 300–321. [CrossRef] [PubMed]
9. Mudie, D.M.; Amidon, G.L.; Amidon, G.E. Physiological Parameters for Oral Delivery and in Vitro Testing. *Mol. Pharm.* **2010**, *7*, 1388–1405. [CrossRef] [PubMed]
10. Dahan, A.; Amidon, G.L. Segmental Dependent Transport of Low Permeability Compounds along the Small Intestine Due to P-Glycoprotein: The Role of Efflux Transport in the Oral Absorption of BCS Class III Drugs. *Mol. Pharm.* **2009**, *6*, 19–28. [CrossRef]
11. Dahan, A.; Sabit, H.; Amidon, G.L. Multiple Efflux Pumps Are Involved in the Transepithelial Transport of Colchicine: Combined Effect of P-Glycoprotein and Multidrug Resistance-Associated Protein 2 Leads to Decreased Intestinal Absorption Throughout the Entire Small Intestine. *Drug Metab. Dispos.* **2009**, *37*, 2028–2036. [CrossRef]
12. Jappar, D.; Wu, S.-P.; Hu, Y.; Smith, D.E. Significance and Regional Dependency of Peptide Transporter (PEPT) 1 in the Intestinal Permeability of Glycylsarcosine: In Situ Single-Pass Perfusion Studies in Wild-Type and Pept1 Knockout Mice. *Drug Metab. Dispos.* **2010**, *38*, 1740–1746. [CrossRef] [PubMed]
13. Tubic-Grozdanis, M.; Hilfinger, J.M.; Amidon, G.L.; Kim, J.S.; Kijek, P.; Staubach, P.; Langguth, P. Pharmacokinetics of the CYP 3A Substrate Simvastatin following Administration of Delayed Versus Immediate Release Oral Dosage Forms. *Pharm. Res.* **2008**, *25*, 1591–1600. [CrossRef]
14. Vaessen, S.F.C.; Van Lipzig, M.M.H.; Pieters, R.H.H.; Krul, C.A.M.; Wortelboer, H.M.; Van De Steeg, E. Regional Expression Levels of Drug Transporters and Metabolizing Enzymes along the Pig and Human Intestinal Tract and Comparison with Caco-2 Cells. *Drug Metab. Dispos.* **2017**, *45*, 353–360. [CrossRef] [PubMed]
15. Jung, K.; Eyerly, B.; Annamalai, T.; Lu, Z.; Saif, L.J. Structural alteration of tight and adherens junctions in villous and crypt epithelium of the small and large intestine of conventional nursing piglets infected with porcine epidemic diarrhea virus. *Vet. Microbiol.* **2015**, *177*, 373–378. [CrossRef] [PubMed]
16. Ozawa, M.; Tsume, Y.; Zur, M.; Dahan, A.; Amidon, G.L. Intestinal Permeability Study of Minoxidil: Assessment of Minoxidil as a High Permeability Reference Drug for Biopharmaceutics Classification. *Mol. Pharm.* **2015**, *12*, 204–211. [CrossRef]
17. Dahan, A.; Lennernäs, H.; Amidon, G.L. The Fraction Dose Absorbed, in Humans, and High Jejunal Human Permeability Relationship. *Mol. Pharm.* **2012**, *9*, 1847–1851. [CrossRef] [PubMed]
18. Lennernäs, H. Regional intestinal drug permeation: Biopharmaceutics and drug development. *Eur. J. Pharm. Sci.* **2014**, *57*, 333–341. [CrossRef] [PubMed]
19. Lennernäs, H. Human in Vivo Regional Intestinal Permeability: Importance for Pharmaceutical Drug Development. *Mol. Pharm.* **2014**, *11*, 12–23. [CrossRef]
20. Olivares-Morales, A.; Lennernäs, H.; Aarons, L.; Rostami-Hodjegan, A. Translating Human Effective Jejunal Intestinal Permeability to Surface-Dependent Intrinsic Permeability: A Pragmatic Method for a More Mechanistic Prediction of Regional Oral Drug Absorption. *AAPS J.* **2015**, *17*, 1177–1192. [CrossRef]
21. Markovic, M.; Zur, M.; Dahan, A.; Cvijić, S. Biopharmaceutical characterization of rebamipide: The role of mucus binding in regional-dependent intestinal permeability. *Eur. J. Pharm. Sci.* **2020**, *152*, 105440. [CrossRef]
22. Bisanz, J.E.; Spanogiannopoulos, P.; Pieper, L.M.; Bustion, A.E.; Turnbaugh, P.J. How to Determine the Role of the Microbiome in Drug Disposition. *Drug Metab. Dispos.* **2018**, *46*, 1588–1595. [CrossRef]
23. Clarke, G.; Sandhu, K.V.; Griffin, B.T.; Dinan, T.G.; Cryan, J.F.; Hyland, N.P. Gut Reactions: Breaking Down Xenobiotic–Microbiome Interactions. *Pharmacol. Rev.* **2019**, *71*, 198–224. [CrossRef]
24. Spanogiannopoulos, P.; Bess, E.N.; Carmody, R.N.; Turnbaugh, P.J. The microbial pharmacists within us: A metagenomic view of xenobiotic metabolism. *Nat. Rev. Microbiol.* **2016**, *14*, 273–287. [CrossRef]
25. Dahan, A.; Beig, A.; Lindley, D.; Miller, J.M. The solubility–permeability interplay and oral drug formulation design: Two heads are better than one. *Adv. Drug Deliv. Rev.* **2016**, *101*, 99–107. [CrossRef] [PubMed]
26. Fine-Shamir, N.; Beig, A.; Dahan, A. Adequate Formulation Approach for Oral Chemotherapy: Etoposide Solubility, Permeability, and Overall Bioavailability from Cosolvent- vs. Vitamin E TPGS-Based Delivery Systems. *Int. J. Pharm.* **2021**. [CrossRef]
27. Lozoya-Agullo, I.; Zur, M.; Beig, A.; Fine, N.; Cohen, Y.; González-Álvarez, M.; Merino-Sanjuán, M.; González-Álvarez, I.; Bermejo, M.; Dahan, A. Segmental-dependent permeability throughout the small intestine following oral drug administration: Single-pass vs. Doluisio approach to in-situ rat perfusion. *Int. J. Pharm.* **2016**, 201–208. [CrossRef]
28. Wolk, O.; Markovic, M.; Porat, D.; Fine-Shamir, N.; Zur, M.; Beig, A.; Dahan, A. Segmental-Dependent Intestinal Drug Permeability: Development and Model Validation of In Silico Predictions Guided by In Vivo Permeability Values. *J. Pharm. Sci.* **2019**, *108*, 316–325. [CrossRef] [PubMed]
29. Teixeira, L.d.; Chagas, T.V.; Alonso, A.; Gonzalez-Alvarez, I.; Bermejo, M.; Polli, J.; Rezende, K.R. Biomimetic Artificial Membrane Permeability Assay over Franz Cell Apparatus Using BCS Model Drugs. *Pharmaceutics* **2020**, *12*, 988. [CrossRef]
30. Lozoya-Agullo, I.; Gonzalez-Alvarez, I.; Zur, M.; Fine-Shamir, N.; Cohen, Y.; Markovic, M.; Garrigues, T.M.; Dahan, A.; Gonzalez-Alvarez, M.; Merino-Sanjuán, M.; et al. Closed-Loop Doluisio (Colon, Small Intestine) and Single-Pass Intestinal Perfusion (Colon, Jejunum) in Rat—Biophysical Model and Predictions Based on Caco-2. *Pharm. Res.* **2017**, *35*, 2. [CrossRef] [PubMed]
31. Pham-The, H.; Cabrera-Pérez, M.Á.; Nam, N.-H.; Castillo-Garit, J.A.; Rasulev, B.; Le-Thi-Thu, H.; Casañola-Martin, G.M. In Silico Assessment of ADME Properties: Advances in Caco-2 Cell Monolayer Permeability Modeling. *Curr. Top. Med. Chem.* **2018**, *18*, 2209–2229. [CrossRef]

32. Pham-The, H.; Garrigues, T.; Bermejo, M.; González-Álvarez, I.; Monteagudo, M.C.; Cabrera-Pérez, M.Á. Provisional Classification and in Silico Study of Biopharmaceutical System Based on Caco-2 Cell Permeability and Dose Number. *Mol. Pharm.* **2013**, *10*, 2445–2461. [CrossRef] [PubMed]
33. Ta, G.H.; Jhang, C.-S.; Weng, C.-F.; Leong, M.K. Development of a Hierarchical Support Vector Regression-Based In Silico Model for Caco-2 Permeability. *Pharmaceutics* **2021**, *13*, 174. [CrossRef]
34. Ruiz-Picazo, A.; Colón-Useche, S.; Perez-Amorós, B.; González-Álvarez, M.; Molina-Martínez, I.; González-Álvarez, I.; García-Arieta, A.; Bermejo, M. Investigation to Explain Bioequivalence Failure in Pravastatin Immediate-Release Products. *Pharmaceutics* **2019**, *11*, 663. [CrossRef]
35. Bermejo, M.; Hens, B.; Dickens, J.; Mudie, D.; Paixão, P.; Tsume, Y.; Shedden, K.; Amidon, G.L. A Mechanistic Physiologically-Based Biopharmaceutics Modeling (PBBM) Approach to Assess the In Vivo Performance of an Orally Administered Drug Product: From IVIVC to IVIVP. *Pharmaceutics* **2020**, *12*, 74. [CrossRef]
36. Markovic, M.; Zur, M.; Ragatsky, I.; Cvijić, S.; Dahan, A. BCS Class IV Oral Drugs and Absorption Windows: Regional-Dependent Intestinal Permeability of Furosemide. *Pharmaceutics* **2020**, *12*, 1175. [CrossRef] [PubMed]
37. Ruiz-Garcia, A.; Tan, W.; Li, J.; Haughey, M.; Masters, J.; Hibma, J.; Lin, S. Pharmacokinetic Models to Characterize the Absorption Phase and the Influence of a Proton Pump Inhibitor on the Overall Exposure of Dacomitinib. *Pharmaceutics* **2020**, *12*, 330. [CrossRef]
38. Dahlgren, D.; Cano-Cebrián, M.-J.; Olander, T.; Hedeland, M.; Sjöblom, M.; Lennernäs, H. Regional Intestinal Drug Permeability and Effects of Permeation Enhancers in Rat. *Pharmaceutics* **2020**, *12*, 242. [CrossRef]
39. Fu, M.; Al-Gousous, J.; Blechar, J.A.; Langguth, P. Enteric Hard Capsules for Targeting the Small Intestine: Positive Correlation between In Vitro Disintegration and Dissolution Times. *Pharmaceutics* **2020**, *12*, 123. [CrossRef] [PubMed]
40. Markovic, M.; Zur, M.; Fine-Shamir, N.; Haimov, E.; González-Álvarez, I.; Dahan, A. Segmental-Dependent Solubility and Permeability as Key Factors Guiding Controlled Release Drug Product Development. *Pharmaceutics* **2020**, *12*, 295. [CrossRef]
41. Christfort, J.F.; Guillot, A.J.; Melero, A.; Thamdrup, L.H.E.; Garrigues, T.M.; Boisen, A.; Zór, K.; Nielsen, L.H. Cubic Microcontainers Improve In Situ Colonic Mucoadhesion and Absorption of Amoxicillin in Rats. *Pharmaceutics* **2020**, *12*, 355. [CrossRef] [PubMed]
42. Pang, K.S.; Peng, H.B.; Noh, K. The Segregated Intestinal Flow Model (SFM) for Drug Absorption and Drug Metabolism: Implications on Intestinal and Liver Metabolism and Drug–Drug Interactions. *Pharmaceutics* **2020**, *12*, 312. [CrossRef] [PubMed]
43. Xie, C.; Jones, K.L.; Rayner, C.K.; Wu, T. Enteroendocrine Hormone Secretion and Metabolic Control: Importance of the Region of the Gut Stimulation. *Pharmaceutics* **2020**, *12*, 790. [CrossRef] [PubMed]