

## Voices in *Molecular Pharmaceutics*: Meet Dr. Zahari Vinarov, Who Unites Physical Chemistry and Pharmacy to Tackle Fundamental and Industrial Biopharmaceutical Challenges



Cite This: *Mol. Pharmaceutics* 2023, 20, 5949–5951



Read Online

ACCESS |

Metrics & More

Article Recommendations

### ■ CURRENT ROLE

I am currently an associate professor, leading several research projects funded by the pharmaceutical industry or public research agencies. One of these projects is a five-year (2022–2027) national grant (the 3D GUT project), which aims to create a personalized, interactive, 3D virtual model of the human stomach and small intestine that can predict the phase distribution, absorption, and food interactions of oral drugs (small molecules, peptides, and RNA/DNA), based on advanced time-, space-, and phase-resolved *in silico* profiling of drug concentrations (Figure 1). To achieve this ambitious goal, our team will (1) capture gastrointestinal anatomy and dynamics via 3D MRI, providing personalization and describing interindividual variability in organ size and shape, (2) use computational fluid dynamics to study the real hydrodynamics at anatomically and physiologically relevant conditions, and (3) integrate all main physicochemical

and biochemical reactions, at colloidal and molecular levels, including advanced formulation behavior, drug dissolution, phase distribution, and permeation. This challenging and highly multidisciplinary effort aims to lead to a novel simulation platform of the upper gastrointestinal tract, opening new horizons in personalized medicine, oral drug absorption, and food effects research, while facilitating the efforts to abolish animal studies.

### ■ CHALLENGES OR BARRIERS

My journey as a scientist at the interface between pharmacy and chemistry started in 2008, as a research assistant in the Department of Chemical and Pharmaceutical Engineering in Sofia University, while still being an undergraduate Pharmacy student. The exposure of the Department to the industry introduced me (as a research team member in >15 projects) to an uncharted territory: the diverse applications of chemical engineering and formulation science.

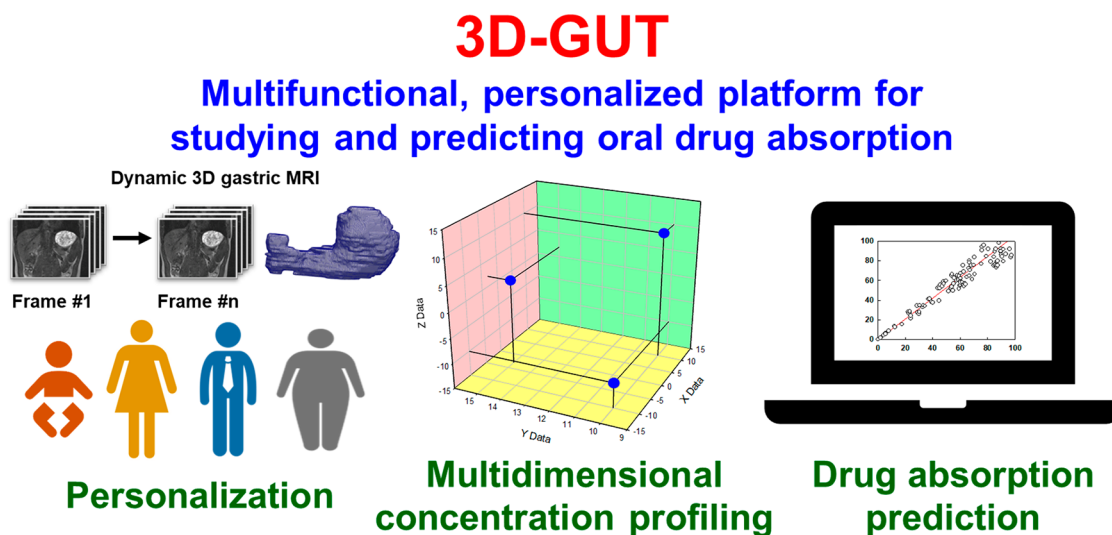
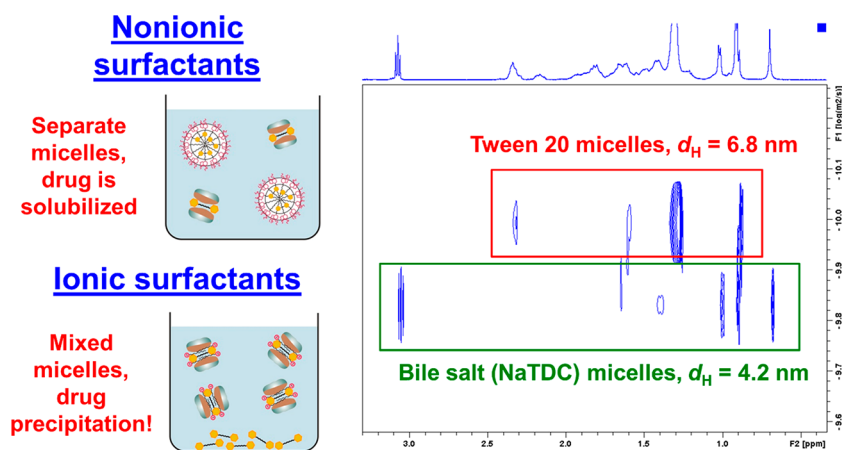


Figure 1. Current main research project (2022–2027).

Published: September 27, 2023





**Figure 2.** DOSY NMR results, illustrating the coexistence of Tween 20 and taurodeoxycholate micelles.

However, although we had long-standing partnerships with chemical companies such as Unilever, BASF, etc., it was difficult to engage the pharmaceutical industry. Reaching out to local players was also impossible, as Bulgaria still lacks the presence of any of the big R&D pharmaceutical companies (only a couple of generic producers are present). The situation changed with the help of an EU project (COST Action UNGAP), which connected us to the European family of drug absorption researchers and later resulted in my postdoc in the group of Professor Patrick Augustijns in KU Leuven, where I worked on a project with Janssen Pharmaceutica. Nowadays, I am back in Sofia University with several ongoing projects with the pharmaceutical industry.

### ■ ONE THING I HOPE TO ACCOMPLISH IN THE FUTURE

I hope that in the coming years I can establish our department and Sofia University among the leaders in oral formulation development and drug absorption.

### ■ A RECENT MOLECULAR PHARMACEUTICS PAPER

The study we published on surfactant–bile interactions in biorelevant media (*Effect of Surfactant–Bile Interactions on the Solubility of Hydrophobic Drugs in Biorelevant Dissolution Media*) provided some particularly interesting insights. We found that nonionic surfactants and bile salt mixtures behave as ideal mixtures in respect to drug solubilization: A linear change in the solubilization capacity as a function of mixture composition was observed. In contrast, ionic surfactants behaved quite differently, exhibiting a sharp decrease in drug solubilization after the addition of minimal concentrations of bile salts. After we demonstrated that mixing the surfactants with pure taurodeoxycholate leads to the same trends, we studied the mechanisms in more detail by nuclear magnetic resonance (NMR) spectroscopy. With the help of diffusion ordered spectroscopy (DOSY), we showed that nonionic surfactant micelles can coexist with bile salt micelles (limited or no mixing), whereas ionic surfactants formed mixed micelles with low drug solubilization capacity with the bile salts, leading to drug precipitation (Figure 2).<sup>1</sup>

Zahari Vinarov [orcid.org/0000-0003-1857-1840](https://orcid.org/0000-0003-1857-1840)

### ■ AUTHOR INFORMATION

Complete contact information is available at:  
<https://pubs.acs.org/10.1021/acs.molpharmaceut.3c00820>

### Notes

Views expressed in this editorial are those of the author and not necessarily the views of the ACS.

### ■ ACKNOWLEDGMENTS

I am grateful to Professors Lynne Taylor and Christel Bergström for the opportunity to share the story of my work in pharmaceutical sciences. I also express my gratitude to Professor Patrick Augustijns for the great discussions and the many opportunities offered during my postdoc in KU Leuven, as well as to my Ph.D. supervisors Professors Slavka Tcholakova and Nikolai Denkov, who taught me how to approach and solve (not exclusively) scientific problems. I am thankful to my industrial collaborators (Jan Bevernage, Christophe Tistaert, George Mihov, Mirko Koziolok, Mark McAllister, and many others) for the great discussions and for the challenging formulation and biopharmaceutical questions we try to answer together. I also acknowledge the support of my colleagues and friends in the Department of Chemical and Pharmaceutical Engineering of Sofia University, without whom I would not be where I am today. I thank my wife, Liliya, for always standing beside me and for her dedication in raising our beautiful daughter, Elia. Finally, I gratefully acknowledge the support of the Bulgarian Ministry of Education and Science, under the National Research Program “VIHREN-2021”, who funds my current main scientific project, the 3D-GUT (No. KP-06-DV-3/15.12.2021).

### ■ REFERENCES

- (1) Vinarov, Z.; Katev, V.; Burdzhiev, N.; Tcholakova, S.; Denkov, N. Effect of Surfactant–Bile Interactions on the Solubility of Hydrophobic Drugs in Biorelevant Dissolution Media. *Mol. Pharmaceutics* **2018**, *15* (12), 5741–5753.
- (2) Vinarov, Z.; Petrova, L.; Tcholakova, S.; Denkov, N. D.; Stoyanov, S. D.; Lips, A. In vitro study of triglyceride lipolysis and phase distribution of the reaction products and cholesterol: effects of calcium and bicarbonate. *Food Funct.* **2012**, *3* (11), 1206–1220.
- (3) Vinarov, Z.; Petkova, Y.; Tcholakova, S.; Denkov, N.; Stoyanov, S.; Pelan, E.; Lips, A. Effects of emulsifier charge and concentration on pancreatic lipolysis. 1. In the absence of bile salts. *Langmuir* **2012**, *28* (21), 8127–8139.
- (4) Vinarov, Z.; Tcholakova, S.; Damyanova, B.; Atanasov, Y.; Denkov, N. D.; Stoyanov, S. D.; Pelan, E.; Lips, A. Effects of emulsifier charge and concentration on pancreatic lipolysis: 2. Interplay of emulsifiers and biles. *Langmuir* **2012**, *28* (33), 12140–12150.

(5) Vinarova, L.; Vinarov, Z.; Damyanova, B.; Tcholakova, S.; Denkov, N.; Stoyanov, S. Mechanisms of cholesterol and saturated fatty acid lowering by Quillaja saponaria extract, studied by in vitro digestion model. *Food Funct.* **2015**, *6* (4), 1319–1330.

(6) Vinarova, L.; Vinarov, Z.; Tcholakova, S.; Denkov, N. D.; Stoyanov, S.; Lips, A. The mechanism of lowering cholesterol absorption by calcium studied by using an in vitro digestion model. *Food Funct.* **2016**, *7* (1), 151–163.

(7) Vinarova, L.; Vinarov, Z.; Atanasov, V.; Pantcheva, I.; Tcholakova, S.; Denkov, N.; Stoyanov, S. Lowering of cholesterol bioaccessibility and serum concentrations by saponins: in vitro and in vivo studies. *Food & function* **2015**, *6* (2), 501–512.

(8) Stoyanova, K.; Vinarov, Z.; Tcholakova, S. Improving Ibuprofen solubility by surfactant-facilitated self-assembly into mixed micelles. *Journal of Drug Delivery Science and Technology* **2016**, *36*, 208–215.

(9) Katev, V.; Vinarov, Z.; Tcholakova, S. Mechanisms of drug solubilization by polar lipids in biorelevant media. *Eur. J. Pharm. Sci.* **2021**, *159*, 105733.

(10) Vinarov, Z.; Gancheva, G.; Katev, V.; Tcholakova, S. S. Albendazole solution formulation via vesicle-to-micelle transition of phospholipid-surfactant aggregates. *Drug Dev. Ind. Pharm.* **2018**, *44* (7), 1130–1138.

(11) Vinarov, Z.; Katev, V.; Radeva, D.; Tcholakova, S.; Denkov, N. D. Micellar solubilization of poorly water-soluble drugs: effect of surfactant and solubilize molecular structure. *Drug Dev. Ind. Pharm.* **2018**, *44* (4), 677–686.

(12) Vinarov, Z.; Gancheva, G.; Burdzhiev, N.; Tcholakova, S. Solubilization of itraconazole by surfactants and phospholipid-surfactant mixtures: interplay of amphiphile structure, pH and electrostatic interactions. *Journal of Drug Delivery Science and Technology* **2020**, *57*, 101688.

(13) Vinarov, Z.; Dobрева, P.; Tcholakova, S. Effect of surfactant molecular structure on Progesterone solubilization. *Journal of Drug Delivery Science and Technology* **2018**, *43*, 44–49.

(14) Vinarov, Z.; Radeva, D.; Katev, V.; Tcholakova, S.; Denkov, N. Solubilisation of hydrophobic drugs by saponins. *Indian J. Pharm. Sci.* **2018**, *80* (4), 709–718.

(15) Vinarov, Z.; Abrahamsson, B.; Artursson, P.; Batchelor, H.; Berben, P.; Bernkop-Schnurch, A.; Butler, J.; Ceulemans, J.; Davies, N.; Dupont, D. Current challenges and future perspectives in oral absorption research: An opinion of the UNGAP network. *Adv. Drug Deliv. Rev.* **2021**, *171*, 289–331.

(16) Vinarov, Z.; Abdallah, M.; Agundez, J.; Allegaert, K.; Basit, A. W.; Braeckmans, M.; Ceulemans, J.; Corsetti, M.; Griffin, B.; Grimm, M.; et al. Impact of gastrointestinal tract variability on oral drug absorption and pharmacokinetics: an UNGAP review. *Eur. J. Pharm. Sci.* **2021**, *162*, 105812.

(17) Boyd, B. J.; Bergstrom, C. A. S.; Vinarov, Z.; Kuentz, M.; Brouwers, J.; Augustijns, P.; Brandl, M.; Bernkop-Schnurch, A.; Shrestha, N.; Preat, V. Successful oral delivery of poorly water-soluble drugs both depends on the intraluminal behavior of drugs and of appropriate advanced drug delivery systems. *Eur. J. Pharm. Sci.* **2019**, *137*, 104967.

(18) O'Shea, J. P.; Augustijns, P.; Brandl, M.; Brayden, D. J.; Brouwers, J.; Griffin, B. T.; Holm, R.; Jacobsen, A. C.; Lennernäs, H.; Vinarov, Z.; et al. Best practices in current models mimicking drug permeability in the gastrointestinal tract - An UNGAP review. *Eur. J. Pharm. Sci.* **2022**, *170*, 106098.