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Editorial

Pilar Bustamante and Her Advances in Thermodynamic and Solubility Parameters

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Pilar Bustamante Martínez, a pioneering figure in the field of Pharmaceutical Technology, obtained her PhD in 1979 from the University of Granada (Spain), where she had begun her research and teaching career in 1976. In 1982, she continued her academic career at the University of Alcalá (Spain), further consolidating her contributions to the field of Pharmaceutical Technology until her retirement in 2010. Throughout these years, Professor Bustamante has left a lasting legacy in the academic and scientific fields, without forgetting her human side, being internationally recognised for her innovative research, visionary leadership and strong commitment to the advancement of pharmaceutical sciences. As such, her career exemplifies a harmonious blend of innovation, education and research, making her a transformative figure in the global pharmaceutical community.

At the heart of Professor Bustamante's academic achievements is her prolific research output, which includes more than 120 peer-reviewed publications in prestigious scientific journals. Her studies have profoundly influenced the fields of drug formulation, solubility and thermodynamics, providing essential frameworks that link theoretical principles with practical applications in pharmaceutical development.[1-8]

Professor Bustamante's pioneering work included the development of theoretical and experimental models to predict the solubility of drugs in solvent mixtures or pure solvents, such as the widely cited study "A modification of the extended Hildebrand approach to predict the solubility of structurally related drugs in solvent mixtures" in 1993.[1,9] These models have revolutionised the design of pharmaceutical formulations, significantly reducing experimental burdens while improving efficiency. A systematic investigation on the solubility behaviour of two polymorphs of mefenamic acid in 1999, "Solubility behavior of polymorphs I and II of mefenamic acid in solvent mixtures"[10,11] and their dissolution and transformation pattern shade a light on this area of research and provided a better understanding of the solubility phenomenon. Her exploration of solubility profiles, included in studies such as "Thermodynamic origin of the solubility profile of drugs showing one or two maxima" in 2002,[12-16] have provided critical insights into solute-solvent interactions. This research has influenced the development of drug delivery systems with complex solubility behaviour, improving bioavailability and therapeutic efficacy. In addition, Prof. Bustamante made significant advances in improving methodologies using solubility parameters, including the Hansen and Hildebrand models. Her innovative techniques, as demonstrated in "A new method to determine the partial solubility parameters of polymers from intrinsic viscosity" in 2005,[14] have enabled accurate predictions on the properties of different materials, such as excipients or polymers, paving the way for the creation of stable and effective pharmaceutical formulations. Her work on the thermodynamic analysis of drugs, particularly in studies such as "Enthalpy-entropy compensation for the solubility of drugs in solvent mixtures: Paracetamol, acetanilide, and nalidixic acid in dioxane-water" in 1998 with 294 citations or in "Thermodynamic analysis and enthalpy-entropy compensation for the solubility of indomethacin in aqueous and non-aqueous mixtures" in 2011[15] with 156 citations, have advanced the understanding of the energetic principles governing drug dissolution processes and have been key in contributing to the understanding of enthalpy-entropy compensation in solvent mixtures.[17-20] Other significant studies focus on the improvement of the Hansen solubility parameter method, such as "The modified extended Hansen method to determine partial solubility parameters of drugs containing a single hydrogen bonding group and their sodium derivatives" in 2000.[21-31] The Hansen solubility parameter is a tool used to predict the solubility of materials by considering three components: dispersion forces, polar and hydrogen bonding interactions. The modified method allowed accurate predictions of the solubility of drugs and excipients in solvent mixtures, contributing to drug formulation and development. This research offered practical applications that would optimise the stability of such materials and improve their solubility. It can be summarised by stating that through her contributions, Professor Bustamante has not only deepened the scientific understanding of solubility

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or thermodynamics, but has also provided critical tools and methodologies that have directly benefited pharmaceutical research and subsequent industrial developments.

Moreover, distinguished projects warranting attention are the article "Relationship between the solubility parameter and the binding of drugs by plasma proteins"[32] that examines the correlation between a drug's physicochemical properties, particularly its solubility, and its affinity for plasma protein binding. This binding significantly influences the drug's pharmacokinetic profile, including its distribution, therapeutic efficacy, and elimination. Understanding this relationship is crucial for optimizing drug design and therapeutic strategies, or the study that elucidates how surfactants like Poloxamer 188 can modulate the thermal behavior and solubility of hydrophobic drugs such as cyclosporin A in aqueous solutions, offering valuable insights for the development of enhanced pharmaceutical formulations.[33] In 2002, Jouyban *et al*.[34] is introduced a cosolvency model derived from Williams and Amidon's excess free energy framework to predict drug solubility across various temperatures using minimal experimental data. This approach offers significant savings in experimental resources, which are often costly and time-consuming. To conclude, other noteworthy studies include the employment of novel solubility prediction models, such as those developed by Machatha *et al*.[35] Additionally, investigations into drug solubility exhibiting phase separation, exemplified by benzocaine and salicylic acid, and the study of drug solubilization in solid dispersions, have significantly advanced our understanding in this domain.[35-38]

Throughout her career, she has collaborated with internationally renowned researchers, such as Dr. Alfred Martin of the University of Texas, renowned for her comprehensive approach to the pharmaceutical sciences, particularly in the field of physical pharmacy.[22,23,39] Their joint work, "Physical Pharmacy", has become an indispensable text in the education of pharmacists and scientists worldwide. Later in her career, she collaborated with Dr. Jerome Barra of the University of Geneva.[24-30,40,41] Their collaboration focused on advancing pharmaceutical research, especially on solubility and drug solubility parameters. Together they contributed valuable insights into dissolution processes and developed innovative methods to improve drug formulations, benefiting both academic research and pharmaceutical industry practices. Dr. Bustamante later collaborated closely with Dr. Fleming Martinez from the University of Colombia, focusing their work on drug solubility prediction models and thermodynamic studies of pharmaceutical systems.[15] Their joint work contributed to the development of new methodologies to improve drug bioavailability and optimise formulations, strengthening academic exchange and promoting applied research.

As a testament to her international influence, Professor Bustamante has been a much sought-after figure in the academic community. She has served as a reviewer, consultant and editor for several journals and has contributed her vast experience to numerous symposia, seminars and conferences, reflecting not only her commitment to academic discourse but also her active participation in the changing landscape of pharmaceutical research.

Beyond her ground-breaking scientific research, Professor Bustamante has spent more than 35 years shaping the future of pharmaceutical sciences through her dedication to education. As a university professor, she embodied the ideals of mentorship, fostering intellectual growth and inspiring countless students to reach their potential. Professor Bustamante's mentorship went far beyond academic instruction. She supervised numerous doctoral theses, guiding young researchers in their pursuit of excellence and fostering a new generation of scientists. A countless list of students at all levels benefited from her participation in conferences, PhD courses, congresses, and thesis tribunals. Her lectures, enriched by her research, seamlessly integrated complex scientific principles with real-world applications. Known for her clarity and accessibility, she inspired students of all levels of experience.

It should be emphasised that the book "Physical Pharmacy", in which he participated, continues to serve as a cornerstone in pharmacy education, providing a comprehensive grounding in the physicochemical principles of drug formulation.[39] Her contribution to the book "Tratado de Tecnología Farmacéutica. Sistemas farmacéuticos" also served to share her knowledge and experience of pharmaceutical development processes with future pharmacy graduates.[42] She cultivated a love of learning among her students, emphasising that education is a continuous journey and encouraging them to pursue excellence with integrity and resilience.

While her scientific and educational contributions are remarkable, Professor Bustamante's legacy is also defined by her exceptional humanity and leadership. Her empathy, kindness and unwavering commitment to her students and colleagues have left an indelible mark on all of us who had the privilege of working with her. Her genuine concern for the well-being of her students, both personally and professionally, distinguished her as a mentor.

Professor Bustamante played a key role in designing the pharmacy curricula at the University of Spain that have shaped the academic landscape of pharmaceutical sciences today. Her efforts ensured that pharmaceutical education remained in tune with the ever-evolving scientific and industrial needs of today's society.

The career of Professor Bustamante is a testament to the transformative power of dedication, innovation and humanity in academia. Her scientific contributions have not only advanced the scientific field, but have also inspired countless researchers, educators and practitioners who have succeeded her. Her remarkable legacy will live on not only through her publications and methodologies, but also through the generations of students and colleagues whose lives she has profoundly impacted. As a mentor,

visionary researcher and educator, Professor Bustamante exemplifies the highest ideals of academic excellence and human connection, leaving a beacon of inspiration for future generations.

Author Contributions

Abolghasem Jouyban: Writing – Review & Editing. **M. Ángeles Peña Fernández:** Writing - Original Draft.

Conflict of Interest

There is no conflict of interest.

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