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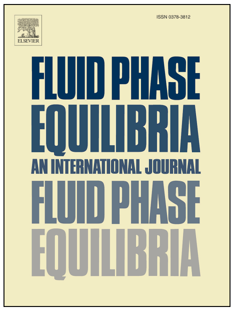

Preface

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Preface

Aqueous Two-Phase Systems (ATPS), also known as aqueous biphasic systems (ABS), were reported for the first time in 1896 when Beijerink observed that liquid-liquid systems could be created by mixing aqueous solutions of gelatin and agar or gelatin and starch. However, it was only in the 50's of the 20^{th} century that ATPS found their place in separation processes, with the works of Albertsson on the creation of ATPS formed by two polymers or a polymer and a salt, and their application in the separation of a plethora of biological products, including proteins, cells, cells organelles, viruses, among others. In the following years, significant attention was given to ATPS as an alternative technique to separate high-value products, among which antibodies have been at the forefront of these works. In addition to traditional ATPS formed by two polymers and/or salts, more recent work has revealed that other combinations of phase-forming components, such as stimuli-responsive polymers, surfactants, ionic liquids and eutectic solvents, can also lead to the creation of ATPS.

At a time where a large number of ATPS have been reported to separate a wide range of compounds, it is probably the right moment to reconsider their potential applications. ATPS can effectively be used to replace currently applied technologies and to address novel fields of application. Although ATPS have been extensively studied for downstream processing, a large fraction of researchers dealing with their application do not use the information on their phase diagrams and composition of the phases, which are essential to understand the products partitioning between the phases. Phase diagrams do not need to be always determined, but at least information from the literature should be used in this respect when analyzing trends on the products partitioning. Furthermore, many authors rely on outdated concepts such as cosmo/chaotropy to rationalize the molecular-level mechanisms responsible for two-phase formation, or molecular/size exclusion for the partitioning of target products between the coexisting phases. Moreover, most literature deals only with the partition of individual compounds, establishing their respective partition coefficients, with no evidence on their selectivity when applied to complex or real matrices. On the other hand, few studies in continuous processes based on ATPS are available, limiting their real applicability at industrial level. Only with this information will we be able to design separation processes based on ATPS, suitable to be applied in large scale industrial processes.

Even if all the required information is available, this does not guarantee that ATPS are really advantageous in the purification of high-value compounds for which there is a high demand, e.g. antioxidants, alkaloids, proteins, enzymes, etc, from real fermentation broths, cell cultures or other complex media. Although significant advances have been reported in the literature, few examples on their industrial application are available. From one side industries will not easily or willingly change their infrastructures and established equipment to use ATPS at their current stage of development, for which a lack of information regarding their characterization and design still remains. On the other side, even if selective and applied in a continuous mode, ATPS will not be a cost-effective strategy unless their phase-forming components could be effectively recycled. ATPS could eventually find their place in the separation of biological products if they show outstanding selectivity to separate high-value products, and for which there is no competitive separation alternative.

At a time where a significant number of works on ATPS is published every year, it is now time to stop and rethink whether these systems have a realistic potential of applicability in separation processes. It is time to reconsider the publication of incremental manuscripts with the partitioning of individual compounds, without evidences on their selectivity or separation performance when applied to real matrices, to stop the use of neoteric solvents such as ionic liquids and eutectic solvents, unless they really show significant advantages over more traditional phase-forming components, and to start figuring out the main mechanisms ruling the solutes partitioning so that a rational process design could be achieved. The use of ionic liquids should not be justified just on their negligible volatility and non-flammability since these properties are also shared by conventional and cheaper polymers and inorganic salts. Given their relatively higher cost, ionic liquids are only relevant to purify high-value compounds if demonstrating superior separation performance, where the designer solvents ability of ionic liquids stands out as the most relevant property of these fluids. When dealing with eutectic mixtures, researchers should have in mind that they are dealing at least with complex quaternary mixtures, meaning that the composition of the phases is more intricate to determine, with clear drawbacks in the process design.

After more than seven decades of research in ATPS mainly in downstream bioprocessing, recent works have shown that they may hold a remarkable potential in the analytical field (including diagnosis), cellular micropatterning and bioprinting, artificial cells production, cells or drugs encapsulation, liquid membranes and batteries, nucleic acids amplification, among others. We do believe that the future of ATPS is highly dependent not only on the development of innovative technologies and science fields, but also in surpassing some of the limitations of current ATPS-based technologies. The knowledge gathered by the ATPS scientific community dealing with downstream bioprocessing can be highly relevant for these novel applications, and interdisciplinary collaborations with sharing of complementary knowledge must be adopted as a practice to prevail towards the successful use and implementation of ATPS in benefit of the society.

This Special Issue covers a series of original research works dealing with ATPS, comprising articles on ATPS fundamentals and phase diagrams determination, on novel phase-forming components (including adjuvants) able to create ATPS, on their application to separate proteins and other high-value products, and on their use in the analytical field. Three relevant reviews also are included, which overview the application of ATPS formed by bio-based ionic liquids, the use of ATPS in continuous mode (from microfluidics to integrated biomanufacturing processes) foreseeing their large-scale application, and a perspective on the future and potential applicability of these exciting systems in novel fields. We are thankful to all authors for contributing with their works and efforts to improve the knowledge on the ATPS field.

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