Title: ***Systemic delivery of biopharmaceuticals: parenteral forever?***

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The subject of systemic delivery of biopharmaceuticals has been discussed in some occasions in Journal of Pharmacy and Bioallied Sciences, which is now in its 11th issue. The last decades have witnessed a strong biotechnological progress, making available many biopharmaceuticals with great therapeutic potential, in many cases promising an undisputed place alongside other established therapies. The meaning of *biopharmaceuticals* is sometimes misleading but, rigorously, this word refers to therapeutic molecules that are biological in nature and manufactured using biotechnology. In this sense, a considerable wide variety of macromolecules is included in this group, from proteins and peptides, to antigens and nucleic acids. Their administration is extremely challenging because of biopharmaceutical and physicochemical limitations, requiring circumventing enzymatic degradation and reducing immune reactions, while ensuring molecular stability and permeability. Parenteral administration appears in this context as an obvious option, as it overcomes some of the referred issues. Actually, to date, the vast majority of marketed biopharmaceuticals is administered by direct injection, usually through intravenous, subcutaneous or intramuscular route. However, the associated cost and patient discomfort, have turned the research efforts of both industrial and academic partners towards alternative possibilities that increase patient compliance.

The compelling need to address the issues mentioned above has prompted the design of a number of strategies that permit needle-free administration, conjugating the identification of alternative routes of administration with the necessary development of adequate drug delivery carriers. Mucosal routes have, thus, been proposed to replace parenteral routes, as mucosal administration might be envisaged to provide a non-invasive systemic pathway. Oral, buccal, nasal, pulmonary, transdermal and vaginal routes are all accepted for systemic biopharmaceutical delivery. However, poor patient acceptability of certain routes like vaginal, reserves their use for local effect only. Nevertheless, the oral, nasal, pulmonary and transdermal routes are taking the forefront of alternative drug delivery, with some technologies already available commercially. Biphasix™ technology (Helix BioPharma) addresses transdermal delivery using liposomes, as do ImuXen® technology (Lipoxen) for oral delivery of DNA and vaccines and AERx® technology (Aradigm Corporation) for pulmonary delivery. Still in pulmonary delivery, Technosphere® technology (Mannkind Corporation) comprises insulin-loaded dry powder microspheres, which are in phase III clinical trials. Importantly, a dry powder formulation of insulin (Exubera®) was previously marketed by Pfizer, but was withdrawn from market by the company, allegedly because of reduced patient adherence to the novel therapeutic strategy. As can be seen, mucosal administration of biopharmaceuticals is inseparable from the task of designing suitable drug carriers. In this sense, as it was stated in a previous Editorial of this journal (Vol. 2, Issue 2, 2010), in many cases nanomedicines seem to have taken advantage, with many reports providing the possibility to make stable effective drugs from unstable biopharmaceuticals. In any case, the carrier is required to maintain the native structure and the biological activity of the encapsulated biopharmaceutical during preparation, delivery and storage.

With such technologies already in the market, and so many others being developed worldwide by academic and industrial researchers, it seems justified to state that the future of biopharmaceutical administration will be progressively shifted from injectable preparations to more user-friendly formulations, with the striking advantage of mucosal routes relying on their non-invasiveness.