The counter ion: expanding excipient functionality.

Apte Shireesh Prakash*

Alcon Research Inc.

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The modulation of physico-chemical and biological processes by electrostatic forces is ubiquitous. Interactions between charged surfaces start, propagate and end processes ranging from the preservation, transcription and translation of genetic information, *trans-membrane* signal transduction, oxidative phosphorylation and energy generation to apoptosis. The fact that one can read this editorial is due to a light induced isomerization event that induces a charge separation of the protonated Schiff base of the chromophore, rhodopsin, from its associated counter ion.

The counter ion is the proverbial *Zelig* because of the underlying universality of its mechanism of action. During manufacturing processes, it affects drug loading into delivery systems, the quality of polymeric bio-actuation devices produced and the refolding of denatured proteins. It is capable of imposing chirality in the manufacture of active pharmaceutical ingredients (APIs), affecting the aggregation state of APIs, thereby modulating programmed release and/or efficacy, altering the quaternary structure of proteins, thus facilitating modulated and temporal drug delivery by ligand activators and possessing the tantalizing potential to convert mutant proteins to their native structure or functionality. It can circumvent cellular membrane barriers (including endo-lysosomal traps) to drug translocation, and significantly enhance the transfection efficiency of genetic or pseudogenetic material. A review by Apte that appears in this issue addresses these diverse effects.

In so far as various permutations and combinations of cationic and anionic counter ions can be combined to form different excipients, ionic liquids being the most manifest examples, excipient properties and function is, in no small measure, dependent upon counter ion components. It would therefore be no exaggeration to state that some pharmaceutical excipients will evolve along the trajectory of the counter ion and counter ion components of excipients will play specific roles in the functionality of APIs. Interestingly, this paradigm of the possibility of 'co-combining' different components (ions) to make up one excipient bears scalable and teleological resemblance to co-processed excipients, where different excipients are co-processed to make up a mixture with altered properties.

Attempts to model the wide gamut of effects of the counter ion after the Hofmeister series have proven tenuous at best, and non-predictive at worst, in part because columbic forces are,

*Alcon Research Inc, 6405 South Freeway, Mail Stop R4-11, Fort Worth, TX 76063, Tel: 817 689 6086, Email: Shireesh.Apte@alconlabs.com

either not the only contributors to, or part of a sequence of contributors to, free energy change. There are relatively few processes where electrical forces, by themselves, are both necessary and sufficient to affect physico-chemical or biological effects. The resulting (relative) paucity of models does nothing to detract from their practical and empirical importance and the contribution of the counter ion as the mediator of these effects.

Excipients have increasingly become 'enablers' of drug delivery and efficacy rather than passive bystanders. Advances in pharmaceutical technology have enabled the ability to deliver specific counter ions (in the form of the counter ion containing excipient) and the API simultaneously to preselected targets in the body. This, coupled with a near universal mechanism of columbic interactions that determine the [API- counter ion] efficacy, can be harnessed to exploit this hitherto unavailable or unrecognized enabling mechanism. New excipients may be assembled by a near inexhaustible supply of different permutations of counter ions and their judicious use in specific situations could potentially drive a renaissance in excipient innovation (and drug delivery and efficacy) despite regulatory stagnation.