

Expanding innovation in the field of pharmaceutical excipients.

Shireesh Prakash Apte*

Alcon Research Inc.

Editorial

KEY WORDS: Excipients, food chemicals, innovation

INTRODUCTION

Much has been written about 'innovation' in excipients. Materials that are primarily manufactured for the food or cosmetic industry can be combined together or derivatised further in various permutations to impart improved properties/functionality to existing materials and/or their combinations, to achieve less excipient variability and to increase excipient understanding (see Figure 1). The approach of mixing and/or derivatizing food ingredients improves manufacturing efficiencies without getting bogged down in the morass of governmental regulation, and imparts synergistic functional properties to existing materials.

The current generation of combined or derivatized excipients primarily increase manufacturing efficiencies, improve API ADME profiles and provide sustained delivery. While these attributes certainly are by no means trivial for the pharmaceutical industry, they are not necessarily conducive to enable *in vivo* delivery or increase *in vivo* efficacy of next generation APIs, which may be defined as

consisting of oligopeptides, peptides and gene modulation/delivery components. It may very well be that these are the only attributes that the current food ingredient combinations *can* change without surfacing on the regulatory radar. On the other hand, it is also possible that some derivatized food ingredients may serendipitously affect such attributes. A prominent example is the discovery that polyoxyethylated castor oil derivatives (and subsequently, the polyoxyethylene-polyoxypropylene block polymers) could modulate cellular efflux pump function. While the ability of food ingredient mixtures or derivatives to modulate more of such 'delivery attributes' should not be underestimated, a re-evaluation of this paradigm is necessary such that 'innovation by design' supersedes 'innovation by serendipity', especially with regard to making pharmaceutical excipients fit for *in vivo* purpose.

Innovation in pharmaceutical ingredients could include prospective design (rather than retrospective discovery) of excipient molecules that actively or passively facilitate the targeted drug delivery of next generation APIs. For example, such excipients could be designed to possess attributes that modulate cell and/or nuclear permeability, efflux pumps, cytochrome

* Alcon Research Inc., 6405 South Freeway, Mail Stop R123, Fort Worth, Texas, 76063, USA, Tel: 8176896086, E-mail shireesh.apte@alconlabs.com

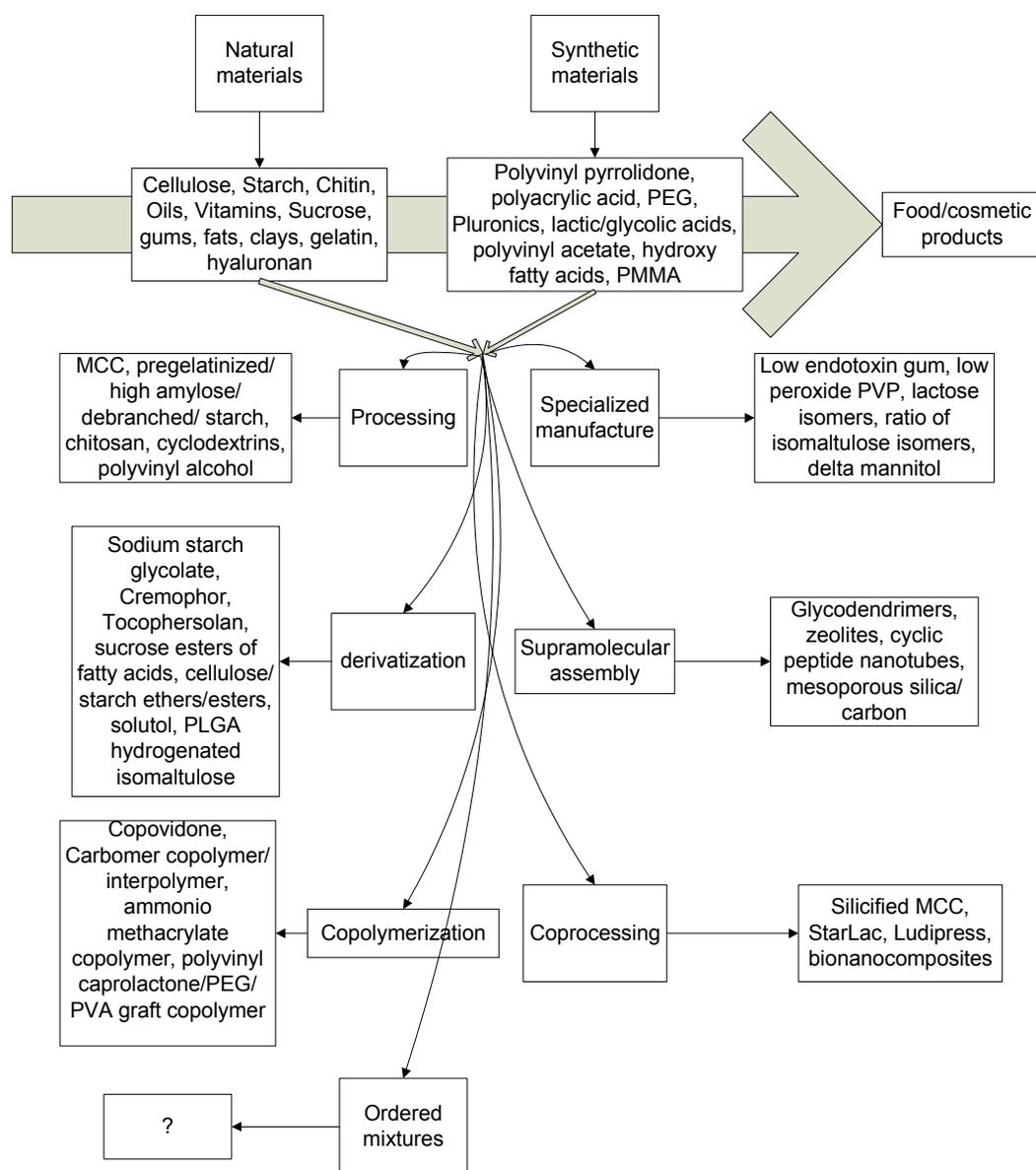


Figure 1 Pharmaceutical excipients as offshoots of the food/cosmetic industry.

P450 enzymes, receptor engagement/internalization and *in vivo* targetability. *In vivo* fit for purpose excipients would enable oral delivery of high molecular weight protein APIs, thermostabilize vaccine products, provide acceptable serum stability (especially for non-glycosylated peptides), suppress API stimulation of innate immune responses and facilitate gene transduction in non-dividing, quiescent cells. Such innovative attributes

would also include minimization of API off-target effects and circumventing the so called 'first pass' phenomenon which is characteristic of many protein or nucleic acid API loaded liposomes or nanoparticles. This is especially important because APIs that rely on cellular processing to exert their therapeutic effect (siRNA for example) have been shown to saturate such pathways at higher concentrations leading to significant morbidity. Dose

minimization is critical toward favorable clinical outcomes. The lack of these attributes signify significant unmet medical needs especially when the 'next generation' of high molecular weight protein, nucleic acid or gene therapies is considered.

Perhaps this is asking too much of molecules that were originally defined as 'inactive ingredients'. Perhaps such 'enabling' attributes are better endowed to APIs themselves via modification of their structures (PEGylation or conjugation). Perhaps such an approach blurs the distinction between an API and an excipient to an unacceptable degree. However, a mere acknowledgment that such *in vivo* fit for purpose molecules *can* be designated as excipients (under carefully formulated considerations); and that they *can* be approved as 'stand alone' entities (with a clear and coherent regulatory pathway); will enable rational design of excipient molecules possessing intricate, defined and built in *in vivo* mechanisms. Their 'innovative attributes' can then complement individual next generation APIs to deliver favorable clinical outcomes. Some examples of such molecules may include ligands for specific receptors, cell penetrating peptides, individual lipid or protein molecules making up exosomes or exosome mimetics, endosome or lysosome destabilizers such as bacterial porins, transfection enhancers including Gemini surfactants, subcellular and/or vesicle traffic modulating excipients/proteins and polyamidoamine PAMAM dendrimers.

Given the regulatory constraints that pharmaceutical excipient manufacturers operate under *a.k.a.* the absence of a regulatory path toward approval of 'stand alone' new excipients, the current paradigm of food ingredient 'mixing and matching' and derivatization and siphoning more succedants from the food industry seems to be the only sustainable business model. With few exceptions, funding, capital expenditure and research on excipients focused on improving clinical outcomes with difficult to

deliver next generation APIs' is mostly non-existent. While it is implicitly recognized that some currently available excipients coincidentally increase efficacy and targetability of some API formulations because of their *in vivo* attribute modulating properties, there seems to be no sense of urgency to explicitly accept and regulate intentionally designed, fit for *in vivo* purpose, excipients. There needs to be recognition that excipient functionality encompasses not only manufacturability and marketability, but also *in vivo* attributes such as facilitation of targetability and increase of efficacy, especially of next generation APIs'.

Innovation in excipients can address excipient functionality, variability and understanding. Another aspect of such innovation could encompass excipients that are deliberately designed to make them fit for *in vivo* purpose, to facilitate cellular (and sub-cellular) specific delivery of next generation APIs that *require* such exquisite targeted delivery in order to be efficacious and safe.

To quote from Thoreau's Walden, "...The man who goes alone can start today; but he who travels with another must wait till that other is ready". It seems high time that the current regulatory paradigm of approving excipients, only as part of a medicinal product, was re-evaluated; and reformulated to approve 'stand alone' excipients. The APIs' are waiting.