Functionality specific excipients influencing manufacturability and/or processing of pharmaceutical dosage forms: a wish list.

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The non-availability of suitable excipients that perform specific functions in manufacturing unit operations or during storage leads to sub-optimal processes and formulations. A 'wish list' of excipients that may alleviate selected sub-optimal processes and formulations is presented below:

1 Excipients that could prevent the adsorption of preservatives or low concentration formulation ingredients, including active pharmaceutical ingredients (API) to filter membranes, fill/transfer tubing and/or primary packaging.

2 Excipients which, when present along with a phase transformed liquid API or an API dissolved in a solvent, could enable the API's 'tunable' precipitation in any particle size, including as a submicron distribution, so that subsequent particle size reduction unit operations would become un-necessary.

3 Amphiphilic excipients which are not prone to auto-oxidation. Auto-oxidation prone excipients are detrimental to the stability of APIs and typically belong to the non ionic polymeric ether class of materials. Amphiphiles such as alkyl saccharides represent feasible non auto-oxidizable alternatives.

4 Excipients that would dissolve suspended APIs upon the application of pressure would potentially enable filtration of coarse suspensions-as-solutions through microbial retentive, 0.2 micron pore size filters. The suspension would then be regenerated upon passage through the filter due to the reduction of pressure and the consequent associated inability of the excipient to modify aqueous properties to enable API dissolution. Processing aids, such as supercritical carbon dioxide exist but possess limited API dissolution capacity. If, upon dissolution, the excipient occupies a significantly lesser volume than when it exists as undissolved solid suspended in water, an increase in pressure will cause dissolution in accordance with Le Chatelier's principle. This is most commonly seen with calcium sulfate whose solubility increases with pressure. Pressure drop is the most common cause of calcium

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sulfate scale in oil well bore and piping. The most intuitive manner in which a solid may be expected to experience a decrease in volume upon dissolution is if the solid were to be a crystalline hydrate encompassing orders of magnitude more water of hydration by weight. Such a solid would probably also need to be amphiphilic so as to dissolve the hydrophobic API. Another potential method would be the addition of volatile amphiphiles to the formulation that can micellize the API upon an increase in pressure and can be driven off in its vapor state upon pressure equalization and perhaps by gentle application of heat.

5 An excipient that would prevent the dissociation of the tetraborohydrate ions from borate-polyol buffers upon dilution, so as to prevent pH changes upon dilution that typically occur during/after sterile filtration.

6 An excipient that would prevent fouling on reactor walls upon bulk sterilization of solutions or suspensions containing polymeric ingredients.

7 It is well known that amphiphilic preservatives such as benzalkonium chloride (BAC) lose their preservation capacity in the presence of high concentrations of surfactants. This effect has been attributed to the partitioning of the into the surfactant micelles. Non-surface active hydrophilic excipients with preservative effect are needed so that they may be formulated in high surfactant micellar solutions without loss of preservative efficacy.

8 Excipients that have a glass transition temperature comparable to mannitol with the additional attribute of being non-crystallizable so as to enable freeze drying of proteins at higher temperatures.

9 Excipients whose crystal size does not depend on the rate of freezing of their solutions. Such excipients (for example) may form large crystals which provide less resistance to mass transfer during the primary drying of lyophilized dosage forms. Lyophilization cycles can be significantly shortened because the solution can be frozen at a faster rate before the initiation of primary drying.

10 Excipient buffers which do not exhibit a pH drift/shift upon freezing their solutions. Aminoalkylsulfonate zwitterions (Good's buffers) present a much lesser pH drift/shift than their inorganic salt counterparts. Zwitterionic buffers are, however, not suitable for the lyophilization of a variety of proteins. Alternative 'Lego®-block' type zwitterions are needed that exhibit a favorable kosmotropic to chaotropic ratio as well as a favorable toxicity profile.

11 Excipients whose ratio of brittleness and plasticity can be modified depending on their manufacturing processing conditions (surface modification). Such excipients with any desired brittleness to plasticity ratio can be paired with specific APIs and/or other excipients to enable direct compression of tablets. Unlike co-processed excipients, a single excipient with the desired compressibility can afford flexibility in the choice of lubricants, binders and disintegrants. Independent modulation of bulk and surface properties to create excipients with an entirely new repertoire of mechanical properties has been proposed before in this Journal (1).

12 A water soluble, non-irritant lubricant for solid dosage forms that is as effective as magnesium stearate with a similar balance of lubricant properties.

13 Amphiphilic surfactants that are capable of forming self emulsifying drug delivery systems (SEDDS) when used at much lower concentrations in combination with oils and cosolvents. This minimizes the toxicity of these dosage forms to the gastrointestinal tract epithelium.

14 Excipients are needed that increase the thermostability of non-freeze dried, live-attenuated vaccines such that the 'cold-chain' is eliminated, at least partially, at the point of use. Heavy water (deuterium oxide) has been shown to increase the thermostability of the poliovirus vaccine. It has been postulated that this thermo-stabilizing effect is due to the greater strength of the non-covalent oxygen-deuterium and nitrogen-deuterium bonds versus the corresponding hydrogen bonds.

15 Excipients that can actively co-associate, as opposed to passively homogeneously mix, multiple (usually a combination of two) APIs, preferably without the aid of melt or solvent processing. Such 'ordered mixtures' prepared with the aid of an excipient(s) can maintain the ratio of the two APIs constant *in vivo* up until receptor engagement. Such excipients are especially needed in inhalation powder delivery of combination drugs.

16 Biopolymers such as polysaccharide gums (xanthan, gellan) that can be manufactured without fermentation (or without using cellular organisms) so as to yield excipients with low endotoxin and extraneous particulate levels.

17 Excipients that can dissolve and stabilize (relatively) hydrophobic proteins.

18 Excipients that can modulate the dielectric constant and/or dipole moment of solvent(s) within a narrow temperature and pressure range. Such excipients (for example) may be used to dissolve hydrophobic APIs in water by inducing a change in its (water's) properties from polar-protic to apolar-protic and/or apolar-aprotic. Supercritical (apolar-protic) water is typically found in submarine hydrothermal systems at temperatures of 350-400°C and pressures of 25-35 MPa. A submarine hot spring hypothesis for the origin of life has been suggested, precisely because the apolar water found under these conditions could be postulated to dissolve apolar precursor molecules. The modulation of hydrogen bonding (and hence polarity and proton donating ability) through the electrochemistry of redox dependent receptors, such as flavins and quinines, has been demonstrated.

It must be recognized that some of the attributes desired of hypothetical excipients may seem unreasonable, given the state of knowledge that exists, as well as, the economic need for indulging in their pursuit. However, a quote attributed to G.B. Shaw in his "Revolutionist's handbook", which was published with the play "Man and Superman" comes to mind:

> "The reasonable man adapts himself to the world; the unreasonable man persists in trying to adapt the world to himself. All progress, therefore, depends on the unreasonable man."

REFERENCES

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