Encyclopedia of Pharmaceutical Technology

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embedded. Depending on the release profile requirement, polymeric excipients are traditionally classified as hydrophilic or hydrophobic. Some representative coating materials include water-soluble resins (e.g, gelatin, starch, polyvinylpyrrolidone, water-soluble celluloses), water-insoluble resins (e.g., polymethacrylate, silicones, water-insoluble celluloses), waxes and lipids (e.g., paraffin, beeswax, stearic acid), enteric resins (e.g., shellac, cellulose acetate phthalate) (63). (Further details on polymers for controlled release systems can be found under "Biopolymers for Controlled Drug Delivery" in the first edition of this encyclopedia series.) Here the focus is on some recent applications of excipients in biologicals.

Live rotavirus vaccine was developed for oral delivery to prevent infections by the virus in young children (64). However, incorporation of live rotavirus into poly (DL-lactide-co-glycolide) microspheres or alginate microcapsules was reported to result in a significant loss of rotavirus infectivity. The loss was reduced by stabilization of the rotavirus vaccine with an excipient blend of cellulose, starch, sucrose, and gelatin at a mass ratio of 30:30:30:10 in granules or tablets (64).

Transforming growth factor (TGF)-betal, a cytoprotectant against the toxicity caused by cell cycle-specific drugs, was encapsulated in alginate beads as a potential oral delivery system to release TGF-betal in the gastrointestinal tract. However, the TGF-betal was interacting with alginate, which prevented the release of the protein. Polyacrylic acid, as a polyanion excipient, was used to shield the TGF-betal from interacting with the alginate (65).

Glucose at concentrations >10% was used to achieve adequate reconstitution of freeze-dried biodegradable poly-Σ-caprolactone nanoparticles with conservation of the encapsulated cyclosporin A (66). Glucose and trehalose were also found to be the most efficient cryoprotectors for the lyophilization process, whereas trehalose was used for spray-drying, in the production of solid lipid nanoparticles (67).

Tetanus toxoid (the vaccine for tetanus) encapsulated in polyester microspheres was produced for single-injection immunization (68, 69). The entrapment efficiency of the protein vaccine was significantly improved by coencapsulation with excipients such as trehalose and (γ-Hydro--Hydroxypropyl cyclodextrin. However, these excipients did not impart stabilizing effect on tetanus toxoid. In contrast, bovine serum albumin was found to be the most prominent stabilizer for protein in the body after administration by injection.

It is important to point out that the stabilizing effects of excipients were sometimes reported for the formulations in vitro rather than in the in vivo conditions. However, the degree of retention of the native protein structure in the dry state may not be a general indication of stability for the 'wetted' solid within polymer controlled-release devices in the body. In the case of tetanus toxoid, it was shown that the extent of structural alternations in the presence of 1:5 (gram excipient:gram protein) sodium chloride, sorbitol, or polyethylene glycol did not correlate with stability conferred toward moisture-induced aggregation (70).

Surfactant and polyethylene glycols (PEG) excipients have been used in microencapsulation of macromolecules for various effects. For example, Tween 20, at the critical micelle concentration and at a molar concentration of protein:surfactant of 1:0.018 or larger, was found to increase the encapsulation efficiency of β-Lactoglobuline in poly (DL-Lactide-co-glycolide) microspheres (71). The initial burst release was reduced with increasing Tween 20 concentration, and the effect was attributed to reduction of the number of pores and channels inside the microspheres. For gene therapy, the release of biologicals encapsulated in microspheres can be significantly improved by adding surfactant during microencapsulation, as recently exemplified by the enhancing effect of polyvinyl alcohol on the release of adenovirus from PLGA microspheres (72). PEG 400 has been used to improve the stability of the protein, nerve growth factor (NGF) during the microencapsulation by a double emulsion method. It stabilized the protein by reducing the contact with the organic solvent in the process. Furthermore, the presence of NaCl in the microencapsulation process has been shown to modify the microsphere structures, leading to a reduction of the initial release rate of NGF (73).

EXCIPIENTS AND FORMULATION INCOMPATIBILITY

During formulation design some excipients may be incompatible with the active ingredient or with other excipients. Excipient incompatibility problems are, in fact, widely published and date back to the mid-1950s. For example, as a tableting excipient, lactose could react via its aldehyde group with both primary (1) and secondary (74) amines by the Maillard-type condensation reaction. Sorbitol, another excipient sugar, is hygroscopic at relative humidity >65%, which should thus be avoided during manufacturing. Calcium salts are other widely used tableting excipients. However, calcium carbonate is incompatible with acids or acidic drugs because of the acid–base chemical reaction. Calcium salts are also incompatible with tetracyclines because of the formation

of calcium–tetracycline complexes. Details of reactivities and incompatibilities of individual excipients are given in Ref. 1. Incompatibility attributable to excipients is commonly studied under accelerated testing conditions or using thermal analyses such as differential scanning calorimetry. However, the results of this rapid testing could be misleading and thus of very limited value (75).

Besides direct excipient–drug interactions, excipients can lead to instability of the active ingredient by an indirect role through moisture distribution. Residual water content is known to affect the stability of solid dosage forms and powders (76). Decomposition of cephalothin sodium and benzylpenicillin potassium decomposition in freeze-dried preparation was believed to be partly attributed to the effect of water binding to excipients (4). The degradation rate of cephalothin sodium increased with the water content of excipients corn starch and celluloses (77). The results were correlated with the water mobility in the presence of the excipients (4, 77). A study of the effect of various excipients on the solid-state crystal transformation of the antimalarial compound mefloquine hydrochloride revealed that microcrystalline cellulose promoted the transformation from form E into form D (78). However, methylcellulose, hydroxyethylcellulose, β-Cyclodextrin, crospovidone, and hydrous lactose had no effect. The effect was again explained by the difference in the water uptake behavior by the excipients. Aspirin was formulated with a sugar diluent containing approximately 8% moisture, which did not cause instability problems (79). This was ascribed to the moisture present in the formulation being unavailable to react with the aspirin. The availability of moisture associated with excipients in a formulation can thus be manipulated to control the hydration rate of the active ingredient as in the case of nitrofurantoin, with crystalline lactose giving the fastest and microcrystalline cellulose giving the slowest rate (80). The rate of hydrolysis of methylprednisolone sodium succinate was higher when cofreeze-dried with mannitol than with lactose (81). This correlated with the rate of crystallization of mannitol in the formulation and its subsequent effect on the water distribution in the solid. The stabilizing potency of excipients on recombinant human albumin against aggregation also correlated with the water-sorbing capacity of the excipients (27).

Instability attributable to excipient-mediated water distribution in solids and powders has been explained by excipient physical properties (21, 82–84). Crystalline materials will not uptake moisture until the deliquescent point is reached. In contrast, amorphous excipients will absorb water until their glass transition temperatures fall below the ambient temperature when the mobility of the molecules has increased so much that excipient crystallization will occur to expel the absorbed water from the crystal lattice. Before crystallization, these excipient materials will act as buffers or sorbents to hold the excess moisture which, depending on the water activity, may not be accessible to the active ingredient that is thus be protected from moisture-mediated decomposition. However, when excipient crystallization occurs, the expelled water will become available to react, leading to instability of the drug.

CONCLUSION

Although excipients are the nonactive ingredients, they are indispensable for the successful production of acceptable solid dosage forms. The important roles played by excipients in tablets and capsules, freeze-dried, and spray-dried powders, as well as powder aerosol formulations, were discussed. Some recent applications of excipients in controlled, release formulations for biologicals were also highlighted. Finally, incompatibility problems attributable to excipients were considered with an emphasis on the indirect role of excipients through moisture distribution.

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