Pharmaceutical excipients as possible adverse reaction triggers

Dr. Petra Eichelsdoerfer, ND, CN, RPh

Medications, whether available over the counter or by prescription, nearly always include ingredients beyond those labeled as "active" ingredients. The manufacturing process necessitates the addition of one or more other ingredients, termed excipients. Although once considered largely inert, there is increasing awareness about excipients' significant contributions to the safety, tolerability, and biological activity of pharmaceutical agents.

Recognition of the need to regulate excipients and include them in product labeling have increased in parallel. In 1995, the International Pharmaceutical Excipients Council defined excipients as "Substances, other than the active drug substance or finished dosage form, which have been appropriately evaluated for safety and are included in a drug delivery system to either aid the processing of the drug delivery system during its manufacture, protect, support, enhance stability, bioavailability, or patient acceptability, assist in product identification, or enhance any other attributes of the overall safety and effectiveness of the drug delivery system during storage or use".[1]

The history of modern pharmaceuticals is rife with examples of excipients that proved toxic. In 1937, Massengill marketed a sulfanilamide elixir in which the less-expensive diethylene glycol replaced the usual propylene glycol and glycerin. Tragically, more than 100 people died from acute renal failure brought on by the diethylene glycol. In recent years, this tragedy repeated itself across South Africa, Bangladesh, Nigeria, Haiti, Panama, and Nigeria when diethylene glycol once again appeared in acetaminophen, cough syrup, and teething powder products.[2] In early 1984, a recently introduced injectable vitamin E product (E-ferol) was associated with severe illness and fatalities in low-birth-weight infants, many of whom exhibited thrombocytopenia, renal dysfunction, hepatomegaly, cholestasis,and ascites. E-ferol was withdrawn from the market after being linked to 38 deaths and 43 cases of severe illness. The symptoms have been attributed to the use of polysorbates as preservatives.[2] After decades-long inclusion in vaccines and numerous vaccine-safety debates, the mercury-derived preservative thimerosal is gradually being phased out.[2] An equally important, if very different issue arose with an extended release formulation of oxycodone, OxyContin. After crushing, this product could be smoked or injected, resulting in very rapid absorption of the full dose of oxycodone. This in turn posed significant overdose risk with the potential for fatality.[3]

These historical examples help illustrate the role of excipients in medicinal products. Despite its nephrotoxicity, diethylene glycol was added to these products because of its solvent properties, while polysorbates and thimerosal are both used as preservatives. In general, excipients receive less regulatory scrutiny than active pharmaceutical ingredients and often excipients have prior approval for use in foods. Continued use of others may be allowed based on decades of use; in the US, they might qualify as "generally recognized as safe" (GRAS). As the 21st Century dawned, the International Pharmaceutical Excipients Council's Safety Committee outlined and introduced new guidelines detailing toxicologic testing of new excipients.[1,2,4]

Interestingly, not all excipients are deliberately added to the final product. Some are impurities left behind by the extraction, synthesis, or purification processes used to produce the active ingredient and others may be added for a wide range of reasons. Excipient selection allows for slow-, timed-, and controlled-release formulations, while enteric coatings protect acid sensitive active ingredients from the low pH gastric environment. Excipients may also allow for longer product shelf-life. For very potent agents, diluents or fillers improve dosing. While colours are often added for appearance, they are also important contributors to product identification. By increasing palatability, sweetening and flavouring agents allow chewable, sublingual, and oral liquid formulations and ease pediatric dosing. In summary, excipients significantly alter bioavailability, pharmacokinetics, stability, appearance, and palatability.[4]

There is, however, a downside to all these additives. A controlled-release formulation of oxycodone, OxyContin, proved readily abusable when snorted or injected – it was easily crushed and dissolved. Recognition of this high abuse potential led to a (US) 2010 reformulation specifically to reduce abuse. The reformulated product is more difficult to cut, chew, break, or crush. The excipient polyethylene oxide forms a viscous gel upon contact with water, so it cannot easily be injected or snorted.[5,6] At present, the Canadian formulation of OxyContin does not contain polyethylene oxide.[7]

Comprehensively detailing the allowable excipients and their functions in this space is impractical. Table 1 summarizes common excipients and their uses in pharmaceutical products.

Table 1 - Properties of Common Excipients[19]

Function	Excipient examples
Coloring agents	Food dyes, including tartrazine (FD & C yellow 5)
Coating agents	
Tablet-coating agents	Fibers (e.g., hydroxypropylmethylcellulose); Waxes
Coating color agents	Food dyes; Titanium dioxide (usually combined with dye)
Coating agents	Fibers (e.g., methylcellulose)
Enteric coating agents	Cellulose; Acetate phthalate
Diluents/fillers/vehicles	Starches; Lactose; Fibers; Vegetable oils
Disintegrants	Starches; Fibers (e.g., microcrystalline cellulose)
Emulsion vehicles	Vegetable and nut oils (e.g., sesame oil, corn oil)
Flavouring agents	Food flavouring agents
Granulating agents	Sucrose; Fibers (e.g., methylcellulose)
Lubricants	Talc, Stearates (e.g., magnesium stearate, stearic acid); Hydrogenated vegetable oils
Preservative	Alcohol, Parabens (methyl, propyl)
Surfactants	Polysorbates
Suspending agents	Gums (e.g., tragacanth, sodium alginate); Fibers (e.g., sodium carboxymethylcellulose)
Thixotropic suspending agent	Gums (e.g., xanthum gum)
Solubilizing agent	Alcohol, Propylene glycol
Sweeteners	Sugars (e.g., sucrose); Polyols (e.g., mannitol, sorbitol); High-intensity sweeteners (e.g., aspartame)

Pharmaceutical products are required to include information on "other ingredients" in the product monograph (also called the package insert). These monographs are provided to pharmacies with every bottle of the product. Many can also be found through online searches of the company websites or by using Health Canada's Drug Product Database. The Canada Vigilance Adverse Reaction Online Database provides information about reported adverse drug reactions, and adverse reactions may be reported directly to Health Canada online. The links for all three websites are included below. Unfortunately, Health Canada's Drug Product Database allows only searches using brand name or active ingredient, posing a challenge to anyone hoping to assemble a list of products that contain or are free of any particular excipient. Table 2 lists examples of pharmaceutical products and a short sampling of the excipients they contain.

Table 2 - Excipient examples from Canadian brand-name pharmaceuticals.[20-26] Excipient origin stated where listed in the product monograph.

Brand Name (generic)	Selected Excipients and other Ingredient Notes
Clavulin (amoxicillin/clavulanic acid)	Aspartame; Dry flavours (golden syrup; orange 1; orange 2; raspberry)[20]
Depo-Testosterone (testosterone cypionate injection USP)	Testosterone synthesized from soy[21]
Fosavance (alendronate sodium/cholecalciferol)	Gelatin; modified corn starch; lactose anhydrous. Gluten-free[22]
PMS Testosterone (testosterone undecanoate capsules)	Outer capsule contains pork gelatin[23]
Prometrium (progesterone capsules)	Peanut oil[24]
Singulair (montelukast)	- 10 mg tablets: Lactose monohydrate; Coating contains carnauba wax, ferric oxide, titanium dioxide, yellow ferric oxide[25] - 4 mg and 5 mg chewable tablets: Aspartame; mannitol; red ferric oxide, cherry flavour[25] - 4 mg oral granules (comprehensive excipient list): - Hydroxypropyl cellulose; magnesium stearate; mannitol[25]
Synthroid (levothyroxine sodium USP)	All strengths contain acacia, confectioner's sugar, lactose, magnesium stearate, povidone, and talc. Colour-coding used to differentiate potency. 50 mcg is the only strength that contains NO colour additives.[26]

Excipients can interact with the pharmaceuticals that they come into contact with. For example, esters may form between cetirizine and polyols (e.g., sorbitol, glycerol) present in liquid formulations.[8] While only a tiny percentage of the cetirizine forms esters, this illustrates how excipients may contribute to, or detract from, stability. Presence or absence of certain excipients may also contribute to abuse potential and others may trigger drug interactions by altering metabolic pathway function. A team of Chinese and Canadian researchers tested 22 common excipients, demonstrating varying degrees of cytochrome P450 3A4 inhibition in both in vitro and in vivo animal models.[9]

Including an excipient that enhances bioavailability through inhibition of metabolic pathways may inadvertently increase toxicity of that or another agent.[9] This practice is not limited to pharmaceutical agents. In the U.S., a number of dietary supplements contain grapefruit (e.g., naringin) and/or black pepper (e.g., piperine) extracts, for the purpose of increasing bioavailability (as stated on the label). Among other mechanisms, these constituents increase drug bioavailability partly through inhibiting CYP 3A4 and p-glycoprotein.[10-14] Grapefruit and black pepper are widely accepted foods and generally considered healthy additions to the diet. Naringin and piperine are both allowable food and natural health product ingredients in Canada.[15] However, as with any food, avoiding these foods or food extracts may be advisable for some people. Avoidance is easy enough if labeling is clear and people are aware of the need to do so.

Beyond potential for interactions or abuse, there are other reasons for concern about excipients. The potential for patient sensitivity or allergy is well worth considering. For example, E-Ferol's toxicity has been ascribed to low birth weight infants' inability to adequately metabolize the polysorbates it contained.[2, 9] Starches and oils from corn, soy, or nuts are common. Logically, these are as equally likely to provoke allergic reactions (e.g., rashes, asthma, anaphylaxis) as the foods they are derived from. Although not always the case, (non-anaphylactoid) symptoms may be related to the site of exposure. Thus, oral products may provoke more gastrointestinal symptoms, where inhaled products may lead to respiratory symptoms.

Lactose and polyols (e.g., sorbitol, mannitol) are also very common excipients. For these excipients, tolerance is often dose-dependent. In other words, while the amount in a single product/dose may be tolerable, this changes if the individual takes multiple products that (each) contain a small amount of the same excipient (e.g., lactose). The unintended additive effect may be significant gastrointestinal distress.[16] High intensity sweeteners such as aspartame and saccharin are also relatively common and may trigger sensitivity reactions, just as they would if consumed in foods.[16] Most allowable colouring agents in Canada are also approved for use in foods. Most are also widely used in the U.S. One example is the coal-tar derivative tartrazine, or FD & C yellow #5. Considered among the more sensitizing of the azo dyes, tartrazine has been heavily studied since the 1970s, yet much remains unclear about tartrazine sensitivity. A 2009 Cochrane review found no clear evidence that eliminating tartrazine had

significant effects on asthma control, unless an individual had proven sensitivity to it.[17] While few countries have evaluated the prevalence of tartrazine sensitivity, it is estimated to be 0.12% in France.[18]

Excipients are far from inert. When evaluating a possible adverse drug reaction, first determine whether the reaction is due to the active ingredient, or possibly an excipient. For example, if the patient has a known corn allergy, and the product in question contains corn starch, s/he could easily be reacting to the starch. Start by asking the patient for more information about their symptoms. Symptoms that resemble a previous reaction the patient recognizes (for example, "I feel like I do when I eat corn"), strongly suggests a possible excipient reaction. Identifying an alternative medication that does not contain the offending excipient may solve the problem. If there are no commercially available alternatives, and the medication is clearly indicated, it may be custom formulated by a compounding pharmacy.

About the Author

Petra Eichelsdoerfer, ND, CN, RPh graduated from the University of Washington and Bastyr University and holds degrees in Pharmacy, Nutrition, and Naturopathic Medicine. She has practiced clinically in community and public health settings, the Washington Poison Center, and taught courses in nutrition, biochemistry, and many other basic and clinical science courses at Bastyr University.

In 2010, Dr Eichelsdoerfer completed a postdoctoral research fellowship funded by a grant through the National Center for Complementary and Alternative Medicine (NCCAM), with projects exploring the prevention and treatment of obesity, cost of a healthy diet, and the human gut microbiome. Areas of clinical and research interest include healthy aging, obesity, gastrointestinal health, traditional/natural diet and healing approaches, and how modern clinical medical practices intersect with those of traditional healing.

Currently a Staff Clinical Pharmacist at the Tulalip Clinical Pharmacy and an Assistant Research Scientist at Bastyr University, Dr Eichelsdoerfer is developing nutrition and integrative medicine projects applicable in a Native American tribal health clinic setting. *drpetra@hotmail.com*

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Helpful links:

Health Canada's home webpage:

www.hc-sc.gc.ca

Canada Department of Justice link to Food and Drug Regulation (C.R.C., c. 870):

http://lois.justice.gc.ca/eng/regulations/C.R.C.,_c._870/page-292.html#h-160

Health Canada's Drug Product Database Online Query (English):

http://webprod.hc-sc.gc.ca/dpd-bdpp/index-eng.jsp

Health Canada Natural Products Ingredients Database. Available online:

http://webprod.hc-sc.gc.ca/nhpid-bdipsn/search-rechercheReq.do?lang=eng.

Canada Vigilance Adverse Reaction Online Database (English):

http://www.hc-sc.gc.ca/dhp-mps/medeff/databasdon/index-eng.php

Report an adverse event online to Health Canada

http://www.hc-sc.gc.ca/dhp-mps/medeff/report-declaration/index-eng.php

US Food and Drug Administration's Inactive Ingredients database:

http://www.fda.gov/drugs/informationondrugs/ucm113978