Excipients in Dietary Supplements: The 'Other Ingredients'

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Many of you may recall having looked at your favorite dietary supplement labels and noticing some unfamiliar "other ingredients". Confused and frustrated as to why these ingredients are in your supplements you may have questioned the quality and purity of the products. You may have asked, "What are these ingredients and are they safe to add to health promoting products?" or, "Will the use of supplements containing these unfamiliar ingredients cause health problems in patients?"

Many of these "other ingredients" are considered inert and are called excipients. Excipients play a vital and also controversial role in the manufacturing of dietary supplements, pharmaceutical drugs and even certain food items. They are defined as "components of a finished drug product other than the active ingredient" and they are added during formulation for specific purposes. Excipients are classified by the function they perform, with the most common categories being: binders, fillers, flavors and sweeteners, coloring agents, and lubricants.[1]

"Other ingredients" do serve an important role in the manufacturing of supplements. For example, binders keep our supplements (especially tablets) from crumbling and shedding. Microcrystalline cellulose and colloids (a substance characterized by evenly dispersed particles within another material) are commonly-used binders that come from vegetarian sources and are considered fibers. Fillers are excipients used to take up empty space in a capsule or tablet. Some suppliers use non-food grade fillers such as talc, which can be easily substituted with food-grade filler such as cellulose, an insoluble plant fiber. Although, talc is generally recognized as safe (GRAS) to use as an anti-caking agent in very small concentrations, some serious health concerns do exist. These health concerns which can be as serious as cancer would only be a concern in individuals with long-term exposure to natural talc or regular vaginal application of talc powder.[2]

Flavors are used when manufacturing liquids and chewables, especially for children and consist of sweeteners such as sorbitol, maltose, sucrose, lactose, glycerin or fructose. Xylitol has grown in popularity as a flavoring agent for chewable and liquid supplements. An article published in *Clinical Pediatrics* gathered information on excipients in forty one chewable/liquid multivitamin and mineral preparations. Sucrose was the most common sweetener, listed as an "other ingredient" in 63% of supplements analyzed. Lactose, glycerin and sorbitol were also popular sweeteners found in the preparations. On average, two sweeteners were found in the preparations analyzed. Many sweeteners found in dietary supplements have dose dependent adverse effects and although the regulations require excipients to be labeled the dosage is not required and as such, some dietary supplement manufacturers choose not to disclose the dosage. For patients with sensitivities (may be immune mediated or the result of direct neurological or gastrointestinal toxicity) to sweeteners such as sugar alcohols it would be best to avoid sweetened supplements or to use capsules.[4]

Coloring is added to products primarily for appearances and identification. Many high quality suppliers will use carrots and beets as food grade coloring agents,[1, 3, 4] but others use agents such as FD&C red # 33 (used primarily in cosmetic products), FD&C yellow #6 (most common dye), FD&C red #40, and FD&C blue #1. FD&C red #33 appears to be relatively non-toxic when used externally, may produce leukocytosis when taken internally, but does not demonstrate mutagenic or carcinogenic properties. FD&C yellow # 6 is an azo dye and can cause anaphylactic reactions, angioedema and contact dermatitis. It should also be used with caution in patients taking aspirin, acetaminophen, sodium benzoate and other azo dyes because of cross reactivity concerns. FD&C red #40 has been shown to produce DNA damage in coloncytes of mice[5] and may be linked to hyperactivity in children.[6] FD&C blue # 1, a triphenylmethane dye has caused bronchoconstriction in asthmatic patients.[7]

Certain excipients are used to allow for better lubrication during processing of dietary supplements. Popular lubricants are magnesium stearate, stearic acid and silicon dioxide. The use of magnesium stearate in dietary supplement manufacturing is controversial. Although magnesium stearate is a cost efficient method to lubricate during manufacturing and keep the supplements from clumping, many individuals are concerned about possible side effects and toxicities. Magnesium stearate is commonly sourced from palm oil and cotton seed oil after it has been hydrogenated and these sources may contain high levels of hazardous pesticides. Additional concerns with magnesium stearate include: overdose (companies using high amounts to speed up the manufacturing process), adverse effects on the immune response, and problems with absorption of nutrients. These concerns would require significantly higher levels of magnesium stearate than what is typically added to produce a dietary supplement.[8, 2] Another controversial excipient is titanium dioxide. It is an inorganic white pigment that is used in supplements as a whitening agent.

Titanium dioxide is a pro-oxidant that is also found in cosmetics, paints, paper, inks, fibers and food. Some individuals believe liver toxicity can result by ingesting titanium dioxide.[3]

You may be wondering, why there is so much fuss about excipients? Over the last decade many recalls and deaths have taken place because of excipient contamination and adulteration all around the world. Quality standards are set by committees such as U.S. Pharmacopeia Convention Inc. and are regulated by Good Manufacturing Practices (GMP) and Good Distribution Practices (GDP) by country specific regulatory agencies. Regional industry associations such as International Pharmaceutical Excipients Council (IPEC) promote voluntary guidance utilized by the industry. Even with these regulations and resources, in 2006, 21 people died in Panama after taking a cough syrup formulated with diethylene glycol that was mislabeled as glycerine. During 1990-1996, a total of 371 people died in Nigeria, India and Haiti because of glycerine contaminated with diethylene glycol. Glycerine is a very common excipient used not only in drug manufacturing, but as a base for botanical syrups and non-alcohol tinctures (especially for children's formulas). These adulterations and contaminations are a result of poor GMP and GDP, and differences in excipient monograph specifications among the major pharmacopoeias (PhEur, JP and USP).[1, 9, 10, 11]

Although it is very challenging to manufacture dietary supplements without the use of excipients, some companies have found ways to employ minimal amounts of natural non-toxic excipients. Some examples of natural excipients included natural polysaccharides. Monosaccharide polymers are inexpensive, highly stable, safe, non-toxic, and hydrophilic and gel forming in nature. These monosaccharide excipients include pectin alginates, starch, gums, and volatile oils.[12] The salt form of alginates, sourced from sea weed, can be used in liposomal delivery systems. Starch acetate can be used to create slow release capsules. Gums, such as guar gum, facilitate controlled drug delivery by releasing the active components in the colon. Gums can also be used to protect active constituents in compaction or compression processes (tablets). Volatile oils can increase the bioavailability of poorly water-soluble actives.

Reputable companies are careful to use only the smallest amounts of the least toxic excipients needed to manufacture dietary supplements. For patients who are hypersensitive it would be advised to consider using vegetable encapsulated supplements, as tablets must be manufactured with excipients. It is hard to find a manufacturer who does not use excipients, however if you keep a close eye on these ingredients you will be able to find companies using food-grade non-toxic excipients (such as: cellulose, beets, carrots or hypo-allergenic plant fibers) that may be more appropriate for your sensitive patients. Lastly, make sure the manufacturer is trustworthy and has an excipient quality control process in place, ask for the results of any audits; this will help you determine whether the supplier is trustworthy. While suppliers are unlikely to share the specific findings from third party certification audits, they will share results from both third party and governmental audits and you can find those on line as well. If you are particularly concerned about the quality of the excipients, you inquire about third party cGMP certification of the suppliers of the excipients. Additionally, you can ask the supplier for the certificate of analysis on their most recent receipt of a particular excipient. This will attest to nature of their quality monitoring of the excipients that they are using in their products.

What's in a capsule?

Gelatin capsule	Ingredients: pharmaceutical grade gelatin (86%) (extracted from animal skin and bone collagen), water (14%)
Gelatin capsule (used in some pharmaceuticals)	Ingredients: pharmaceutical grade gelatin (usually over 85%, extracted from animal skin and bone collagen), water (approx. 13%), methylparaben (0.6%), propylparaben (0.1%), sodium lauryl sulphate (0.1%), coloring (optional)
VegiCap (Capsule Connection® and Capsugel®)	Ingredients: hydroxypropylmethylcellulose, also known as hypromellose (derived from vegetable cellulose) (92%), water (8%), glycerin (optional), coloring (optional)
NPcaps (Capsugel®)	Ingredients: pullulan (water-soluble polysaccharide of vegetable origin) (92%), water (8%), glycerin (optional), coloring (optional)
Caplet also referred to as Gelcap	Ingredients: tablet covered with a layer of gelatin
Softgel	Ingredients: gelatin (animal derived or vegetable origin), plasticizers, water, coloring (optional)

Note: All empty capsules should be tested free of heavy metals, microbiological organisms, loss on drying, viscosity, parabens, ethylenes. The consumer should make sure that the manufacturer has done the due diligence and has confirmed that they are using paraben-free gelatin capsules.

Natural Health Products Information Resources

Canada
Health Canada Natural Health Product Regulations
www.hc-sc.gc.ca/dhp-mps/prodnatur/about-apropos/index-eng.php

United States
Food and Drug Administration's Overview of Dietary Supplements
www.fda.gov/Food/DietarySupplements/ConsumerInformation/ucm110417.htm

Clinician Considerations for Assessing Dietary Supplement Quality (Natural Medicine Journal) and Supplier Certification Questionnaire Compliance Guide
http://www.naturalmedicinejournal.com/article_content.asp?edition=1&section=4&article=107

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References

1. *International Pharmaceutical Excipients Council of the Americas*. N.P. 2009. Web accessed 05 May 2011. http://ipecamericas.org.
2. No Author listed. Talcum Powder and Cancer. Web accessed 13 May 2011. Last Revised 11/04/2010. http://www.cancer.org/Cancer/CancerCauses/OtherCarcinogens/AtHome/talcum-powder-and-cancer
3. No author listed. "What are excipients?" *HealthLine*. Web accessed 08 May 2011.
4. Frampton A. "Excipients: An Overview" Now. Web accessed 08 May 2011
5. Shimada C, Kano K, Sasaki YF, Sato I, Tsudua S. Differential colon DNA damage induced by azo food additives between rats and mice. *J Toxicol Sci*. 2010;35(4):547-54.
6. Boris M, Mandel FS. Foods and additives are common causes of the attention deficit hyperactive disorder in children. *Ann Allergy*. 1994 May;72(5):462-8.
7. Kumar, Ashir et al. Sweeteners, Dyes, and other Excipients in Vitamin and Mineral Preparations. *Clin Pediatr* 1996 35:443
8. *Encyclopædia Britannica*. 2006. Encyclopædia Britannica Online, 2011. Web accessed 09 May 2011. <http://www.britannica.com/EBchecked/topic/564584/stearic-acid>.
9. USP International Excipient Workshop. N.P., 2011. Web accessed 05 May 2011.http://www.usp.org/meetings/workshops/internationalExcipientWorkshop.html
10. USP Guidelines for Submitting Requests for Revision to USP-NF. N.P. Web accessed 03 May 2011. http://www.usp.org/pdf/EN/USPNF/revisionHistory.pdf
11. McGlue, Kevin et al. European Excipient Regulation: Implications for Manufacturers and Suppliers. *Innovations in Pharmaceutical Technology*. 2007. Web accessed 05 May, 2011. http://www.iptonline.com/articles/public/IPT_23_p74nonprint.pdf
12. Shirwaikar A, Shirwaikar A, Prabu SL, Kumar GA. Herbal excipients in novel drug delivery systems. *Indian J Pharm Sci*. 2008 Jul-Aug;70(4):415-22.