A fishy aftertaste and unpleasant burps may deter consumers from taking fish oil supplements. There are several ways manufacturers can minimize these disagreeable effects to promote compliance. This article compares the disintegration performance of softgels that employ two commercially available options.

Fish oil supplements are a good source of omega-3 fatty acids and are selling very well thanks in part to the recommendation of the American Heart Association. But many consumers forego the potential health benefits of fish oil because they dislike the fishy aftertaste. Plus, when fish oil softgels dissolve prematurely—in the stomach instead of the small intestine—consumers may experience unpleasant fishy burps and stop taking the supplements.

Applying a coating that delays dissolution of the softgel until it reaches the small intestine can prevent these undesirable side effects and promote compliance. In addition, a coating enhances stability and overall product performance because it protects the softgel from moisture.

Although enteric coating systems for drug products are well established [1], the polymers commonly used in those coatings are not approved for use in dietary supplements or foods [2]. Formulators thus face the challenge of minimizing the unpleasant aftertaste and burps without using pharmaceutical coatings. After briefly reviewing the laws governing dietary-supplement ingredients, this article compares the disintegration performance of fish oil softgels made using two commercially available enteric technologies.

**The ABCs of GRAS**

All non-dietary ingredients used in dietary supplements must be listed as an FDA-approved food additive in 21 CFR or be deemed “generally recognized as safe” (GRAS) for their intended uses and exposure levels. Under sections 201 and 409 of the Federal Food, Drug, and Cosmetic Act, any substance intentionally added to food is deemed a food additive and thus subject to premarket review and approval by the FDA. An exception can be made when a substance is generally recognized by qualified experts as being adequately safe under the conditions of its intended use.

Furthermore, a GRAS material can either be self-affirmed as such by a panel of experts or a GRAS notice can be submitted to the FDA for approval. A GRAS notice submission requires a detailed summary of the data substantiating that the use of the specified ingredient is GRAS and thus exempt from pre-market approval requirements. If the FDA finds no problems with the summary data, it will confer a “no objection” opinion. That is not, however, the same as the FDA approving a specific use of the material, which requires a complete food-additive petition.

Therein lies a common point of confusion in the dietary-supplement industry: A non-dietary ingredient may be GRAS in some applications, but not necessarily GRAS for dietary supplements. That’s because the ingredient must be evaluated and approved specifically for its use in supplement applications at the intended use levels and for a specific associated daily exposure. Use in a different food category, a higher level of use, and/or a higher daily exposure would require a GRAS panel to extend the original GRAS report to cover such use in a dietary supplement.

Additionally, the specifications of a material must match the specifications of the original material reviewed in the GRAS panel’s assessment. While one supplier may have self-affirmed GRAS status for its particular material, that status cannot be used to justify including the same material from another supplier in the dietary supplement. Therefore, it is essential for supplement manufacturers using GRAS ingredients in their formulations to obtain the GRAS report or summary information for the specific material they are using and for its specific intended use and exposure level.

Approved for pharma, not for food

Methacrylic acid copolymer type C (MACC) and polyvinyl acetate phthalate (PVAP) are commonly used in enteric pharmaceutical applications. They are not listed food additives in 21 CFR, and no GRAS notices for them appear on the FDA’s website.

In light of the regulatory limitations on these enteric polymers, formulators of dietary supplements have turned to GRAS gastro-protective film coatings. One option is shellac-based coatings. Shellac, a natural resin secreted by the insect *kerria lacca* (lac beetle), is insoluble in acidic conditions and soluble at higher pH levels [3]. Due to its insolubility in water, shellac is typically used in solvent-
based solutions. However, shellac has stability limitations that make it a poor choice to mask the taste of fish oil.

But other products are available. In 2003, Colorcon launched a delayed-release (DR) coating system for dietary supplements that meets regulatory requirements in North America and Europe and that uses ingredients that are approved as food additives and/or have self-affirmed GRAS status for use in dietary supplements. The coating, called Nutrateric, combines Surelease—an aqueous ethylcellulose (EC) dispersion—with a nutritional enteric component called NS Enteric. EC is a water-insoluble pH-independent polymer that forms a non-eroding diffusion barrier, and the enteric additive functions as a pH-dependent pore-former within the EC film to delay release. As a clear formulation, the coating is 85 percent aqueous EC dispersion and 15 percent enteric additive, hydrated to a 10 percent solids concentration. Pigmented versions are also available.

This DR coating system is easily prepared. First, the pH-dependent pore-former is dispersed in room-temperature de-ionized water under low shear and mixed for 60 to 90 minutes. The aqueous EC dispersion is then added to the solution and mixed slowly for an additional 15 minutes. It is then ready for use, typically at a theoretical weight gain of 3 to 4 percent on softgels using standard coating equipment and standard coating parameters.

Another method of delaying the release of softgels is to use an anti-reflux technology. It typically comprises a gastro-resistant natural polymer (such as pectin), a film-forming natural polymer and, optionally, a gelling agent. Anti-reflux technology cross-links the gelatin in the softgel, allowing it to remain intact longer after ingestion [4].

Determining how well these two approaches work requires testing, and a test method listed in USP 35-NF 30—<2040> Disintegration and Dissolution of Dietary Supplements, Delayed Release Tablets [5]—is well suited to the task. It calls for reciprocating coated softgels (n = 6) for 1 hour in simulated gastric fluid (SGF) at 37° ±2°C. If the softgels remain intact over that period and show no evidence of disintegration, cracking, or softening, they are then reciprocated in simulated intestinal fluid (SIF) at 37° ±2°C until rupture. The tests are performed in Apparatus B, which is required for capsules longer than 18 millimeters. The SGF and SIF are prepared in accordance with USP [6].

**Comparing performance**

Commercially available fish oil softgels from three different manufacturers that use the anti-reflux technology were tested for disintegration. The label of one product claimed an “all natural enteric” and “no fishy aftertaste.” Six softgels of this product were placed in the SGF and failed after 7 minutes (Figure 1a).

The label of the second product made similar claims as the first: “all natural enteric” and “no fishy aftertaste.” Again, six softgels were tested for DR disintegration in SGF and failed after 30 minutes (Figure 1b).

The third product tested failed after 20 minutes (Figure 1c).
Rupture in SGF indicates that the softgels would not remain intact in the low pH of the stomach and could leave consumers with a fishy aftertaste and burps. This could diminish patient compliance, and thus diminish the health benefits from the fish oil.

Two brands of commercially available fish oil softgels coated with our aqueous EC dispersion containing the pH-dependent pore-former were also tested for DR performance. Six softgels from each manufacturer were tested in the SGF, similar to the testing conducted on products that used the anti-reflux technology. Each of the six DR coated softgels was weighed prior to disintegration testing. After weighing, all were placed in the SGF for 1 hour, and both brands stayed intact (Figure 2).

The softgels were then removed from the SGF, blotted dry, and re-weighed to determine how much acid uptake occurred during testing. The percentage weight gain of the softgels is reported as percentage of acid uptake, and an uptake of less than 10 percent is typically acceptable. In this case, uptake for both sets of softgels was less than 5 percent. After weighing and drying, the softgels were reciprocated in SIF at 37°C ±2°C until they ruptured, which took less than 60 minutes.

In previously published work [7], we evaluated the stability of fish oil softgels bearing an EC-based coating. The fish oil softgels were coated to a 4 percent theoretical weight gain in a 24-inch-diameter fully perforated, side-vented coating pan and then packaged in 100-cubic-centimeter induction-sealed HPDE bottles and stored in intermediate (30°C/65 percent relative humidity (RH)) conditions for 12 months and accelerated conditions (40°C/75 percent RH) for 6 months. The softgels with the EC-based coating system were assessed for DR performance after 0, 3, 6, and 12 months of storage. At each time point, the samples passed DR disintegration testing, remaining completely intact without any sign of cracking or splitting after 1 hour in SGF. All capsules were transferred to SIF and disintegrated completely. The stability of these DR-coated softgels ensures that users will avoid the undesirable aftertaste and burps of fish oil while obtaining the benefit of these supplements.

We have also demonstrated the ability to coat softgels with the EC and pH-dependent pore-former system in a continuous coating process [8]. In that work, softgels were coated in a 13.3-foot-long, 24-inch-diameter continuous coating pan. Three trials were done. The theoretical weight gain of the EC-based coating applied, as well as the throughput of the softgels, varied in each trial. During all three trials in the continuous coater, samples of the coated softgels were taken every 5 minutes. Each sample was tested for gastric protection in SGF for 1 hour, and each passed DR disintegration testing.

References
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