

Co-processed Excipients

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ABSTRACT This *Stimuli* article summarizes the thinking of the USP Excipient Monographs 2 Expert Committee and USP staff regarding a class of excipients—collectively labeled *co-processed excipients*—that have been and continue to be introduced into the *National Formulary (NF)*. This article presents some suggested criteria for acceptance of such monograph proposals into *NF* and solicits public input.

INTRODUCTION

In recent years drug formulation scientists have recognized that single-component excipients do not always provide the requisite performance to allow certain active pharmaceutical ingredients to be formulated or manufactured adequately. In response to these deficiencies, drug formulation scientists have relied on increasing numbers of combination excipients introduced by excipient manufacturers into the commercial market. Combination excipients fall into two broad categories: physical mixtures and co-processed excipients.

Physical mixtures, as the name suggests, are simple admixtures of two or more excipients typically produced by short duration low-shear processing. They may be either liquids or solids and are generally used for convenience rather than for facilitating the manufacturing process or improving the resultant pharmaceutical product. Examples of such physical mixtures include immediate-release film coating powders for dispersion that reduce the time required to prepare film coating suspensions and to minimize color variation of the final product. Such physical mixtures are not appropriate for consideration for *National Formulary (NF)* monographs because the individual components are isolated (distinct and intact) before mixing; i.e., the manufacturing process of each of the individual components has been taken to completion, and consequently these components can be adequately controlled before mixing.

Co-processed excipients are combinations of two or more excipients that possess performance advantages that cannot be achieved using a physical admixture of the same combination of excipients. Typically they are produced using some form of specialized manufacturing process. The performance benefits relate to the manufacture or performance of the finished pharmaceutical product. This improvement in performance has been a primary driver for the introduction of co-processed excipients into the marketplace. Co-processed excipients

are appropriate for consideration as new monographs because one or more of the components may be formed in situ, or the component may not be isolated prior to co-processing. That is, the manufacturing process for one component may not have been taken to completion before the addition of the other components, and/or the co-processed excipient combination cannot be adequately controlled using the monograph tests for the individual component excipients.

Because many co-processed excipients contain a macromolecular excipient as one of the constituents, responsibility for reviewing these monographs and recommending them for inclusion in *NF* falls within the purview of the EM2 Expert Committee, one of three Expert Committees that set excipient standards for *NF* in USP's Council of Experts.^d Recently there has been increased interest in *NF* monographs for co-processed excipients. The Expert Committee is therefore addressing the more general question of compendial acceptance of these types of excipients. To this end the EM2 Expert Committee believes that guidelines for the acceptance of monograph proposals for co-processed excipients would be useful.

CURRENT STATUS OF CO-PROCESSED EXCIPIENT MONOGRAPHS IN *NF*

During the past 20 years, several monographs, each of which presents a co-processed combination of existing excipients, have appeared in *NF*. These excipients may be either liquids or solids. *Table 1* lists several examples of co-processed excipient combinations included in *NF* 27 (2009). The co-processed excipient monographs listed in *Table 1* meet current *NF* submission requirements as defined by the following: Each of them is either included in an approved drug application (in the FDA inactive ingredient database) or has a Generally Recognized as Safe (GRAS) designation.

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^d The other two Expert Committees that set excipient standards for *NF* are: Excipient Monographs 1 Expert Committee, which works with small-molecule excipients, and Excipient General Chapter Expert Committee, which prepares General Chapters for excipients.

Table 1. Co-processed Excipients

Name	Form
Ammonio Methacrylate Copolymer Dispersion	Liquid
Ethyl Acrylate and Methyl Methacrylate Copolymer Dispersion	
Ethylcellulose Aqueous Dispersion	
Methacrylic Acid Copolymer Dispersion	
Microcrystalline Cellulose and Carboxymethylcellulose	Solid

The excipients shown in *Table 1* typically are manufactured using some type of specialized manufacturing process such as high-shear dispersion, granulation, spray drying, or melt extrusion. Such combination excipients produced using these specialized manufacturing processes are commonly called co-processed excipients (1–4). Researchers have reported that these co-processed excipients, when incorporated into the finished product, offer one or more improvements in performance in comparison with the corresponding physical admixtures of the constituent excipients or individual components (5).

RECOMMENDATIONS FROM USP EM2 EXPERT COMMITTEE

The EM2 Expert Committee together with involved USP staff has considered the issues regarding co-processed excipients, especially for solid forms, during several years of monograph development and in collaboration and discussion with monograph sponsors. The Expert Committee has formulated the following guidelines that may help determine whether or not such combination excipients are co-processed and whether they will be eligible to be considered for a *NF* monograph. The Expert Committee welcomes comments regarding these guidelines.

Due to the complex nature of co-processed excipients and the diverse composition of their individual constituents, the Expert Committee is unable to propose a single test or other criterion that can be applied to distinguish these co-processed excipients from their corresponding simple physical admixtures. The committee will therefore evaluate *NF* submissions for co-processed excipients on a case-by-case basis using the following criteria:

1. A co-processed excipient is a combination of existing pharmacopeial excipients, and it must be distinguishable—in at least one non-performance-related property—from the admixture obtained by physically mixing the corresponding constituent excipients. A co-processed excipient typically is produced by some specialized manufacturing process such as high-shear dispersion, granulation, spray drying, or melt extrusion. When it is submitted as a potential *NF* monograph, information relating to its quality must meet current *NF* submission requirements: The claimed co-processed excipient is either in-

cluded in an FDA-approved drug application or has a GRAS designation or is under special consideration by the Council of Experts.

2. A physical mixture of the various excipient components—which have not been individually modified in order to change their inherent thermodynamic state prior to being physically mixed—will not quantitatively exhibit one or more characteristics of the co-processed excipient. Co-processed excipients demonstrate one or more different properties regardless of whether a comparative analysis is performed using the physical mixture as is or using a sample of the physical mixture whose particle size distribution is very similar to that of the co-processed excipient. This or other characteristics of the co-processed excipient can be determined by a suitable test method.
3. The physical or chemical characteristic(s) of the co-processed excipient that differ from those of the physical mixture may cause or may be correlated with improvements in the performance of the finished product. However, these unique characteristic(s) must be inherent, demonstrably analyzable, and quantitatively different in the co-processed excipient itself *before* incorporation into the finished product. Thus, if the proposed co-processed excipient does not exhibit any analytical differences from the physical mixture, then it may not be considered a co-processed excipient even if it alters the performance of the finished product.
4. At least one of the components of the co-processed excipient is capable of being analyzed qualitatively and quantitatively in the co-processed state, i.e., without the use of any specific physical or chemical methods to separate the components of the co-processed excipient before analysis of the individual component(s).
5. No unintended covalently bonded chemical entity is formed when the individual ingredients are mixed to form the co-processed excipient. The absence of any chemical reaction(s) between individual ingredients in the co-processed excipient must be analytically demonstrated initially and over the proposed storage period of the co-processed excipient. However, intentional *in situ* salt formation, or formation of a known excipient by *in situ* polymerization or covalent cross-linking would be allowed.
6. The individual ingredients used in a co-processed admixture must have *USP–NF* monographs, or at least monograph proposals published in *Pharmacopeial Forum* as part of in-process revision. This does not necessarily imply that those individual ingredients must demonstrably meet monograph specifications in *USP–NF* before being incorporated or processed into the co-processed excipient. Indeed, this may not be possible because one or more individual component(s) of the co-processed excipient may not be capable of being isolated before co-processing.

However, the proposed co-processed excipient cannot be considered for inclusion as a monograph in *NF* if its production or manufacture involves incorporation of a noncompensial ingredient. In such cases, the co-processed excipient is excluded from *NF* regardless of whether or not the noncompensial ingredient is isolated before co-processing. Thus, if a sponsor wishes to propose a monograph for a co-processed excipient that contains a noncompensial excipient, the sponsor would first be required to secure an approved *NF* monograph for the noncompensial excipient.

CASE STUDIES

Since 2005 the EM2 Expert Committee has been working with a monograph sponsor to develop a new monograph titled Silicified Microcrystalline Cellulose (6). This excipient is recorded in the FDA inactive ingredient database as Prosolv, Prosolv 50, Prosolv 90, Prosolv HD 90, Prosolv SMCC 50, or Prosolv SMCC 90. It is categorized as a co-processed excipient (3). The monograph for this excipient underscores the importance of identification tests for this type of material. In the proposed Silicified Microcrystalline Cellulose monograph, four individual tests are used to identify this co-processed excipient. They are Fourier-transform infrared spectroscopy (FTIR), wet chemical tests for cellulose and silicon, and a *Silica dispersion uniformity test*, which is used to distinguish the co-processed excipient from the equivalent physical admixture of microcrystalline cellulose and silica. FTIR is useful for providing a confirmation of molecular structure. The FTIR measurement ensures that the material is predominantly a microcrystalline cellulose-like material. Additional identification tests in combination provide differentiation among microcrystalline cellulose, silicified microcrystalline cellulose, and a physical admixture of microcrystalline cellulose and colloidal silicon dioxide.

The EM2 Expert Committee believes that Silicified Microcrystalline Cellulose meets all the criteria for inclusion as a separate monograph in *NF* based on the criteria listed above under Recommendations.

The EM2 expert committee also published a new monograph: Polyvinyl Acetate Dispersion (7). This material is a liquid co-processed excipient manufactured by an in situ polymerization process. The polymerization occurs in the presence of emulsifiers and stabilizers in water to form the dispersion, which is different from a physical admixture because the monomer, vinyl acetate, is polymerized during the manufacturing process. This excipient is used in an FDA-approved drug product, although it is not yet recorded in the FDA inactive ingredient database. Its application was confirmed by a US drug company. In addition to the major component, polyvinyl acetate, some minor components in the disper-

sion are povidone and sodium lauryl sulfate. *NF* includes monographs for Povidone and Sodium Lauryl Sulfate, as well as Polyvinyl Acetate. In 2008 the EM2 Expert Committee published a new monograph proposal for Polyvinyl Acetate (8) to replace a previous proposal (9). In the new monograph proposal for Polyvinyl Acetate Dispersion, the Expert Committee recommended strengthening the *Labeling* section: Any added surface active agent or stabilizer should be named, and its quantity should be provided. The Expert Committee further recommended that a test for Povidone should be included under a section called Stabilizers or Surface Active Agents and a limit test should be used.

The EM2 Expert Committee believes that Polyvinyl Acetate Dispersion also meets the criteria for inclusion as a separate monograph in *NF* based on the Recommendations listed above.

SUMMARY

The EM2 Expert Committee continues to work on developing/updating monographs that satisfy current regulatory requirements and industrial practices and that appear to be scientifically sound. The development of guidelines to facilitate the incorporation of co-processed excipients in *NF* and to differentiate them from physical mixtures promises to be a challenging and interesting topic for the EM2 Expert Committee for the remainder of the current cycle and for new Expert Committees and/or Expert Panels in coming cycles. With staff, the USP EM2 Expert Committee welcomes public comments on these proposals (please send comments to hw@usp.org).

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