Food and Agriculture Organization of the United Nations

80th JECFA - Chemical and Technical Assessment (CTA), 2015

POLYVINYL ALCOHOL (PVA)-POLYETHYLENE GLYCOL (PEG) GRAFT CO-POLYMER

Chemical and Technical Assessment (CTA)

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1. Summary

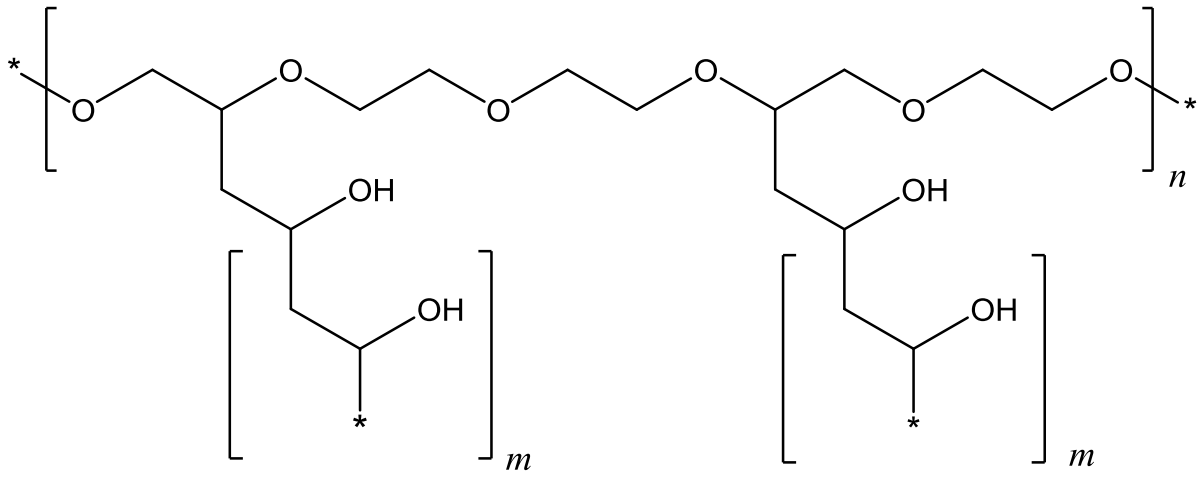
This Chemical and Technical Assessment summarizes data and information on polyvinyl alcohol (PVA)-polyethylene glycol (PEG) graft co-polymer (PVA-PEG graft co-polymer) as provided by the sponsor BASF in response to the call for data to the 80th Joint FAO/WHO Expert Committee Meeting on Food Additives (JECFA).

PVA-PEG graft co-polymer is a synthetic branched co-polymer consisting of a main backbone of PEG and two to three side chains of PVA. The co-polymer is manufactured by grafting polyvinyl acetate chains onto the PEG backbone which are then hydrolysed to form the PVA side chains. The final co-polymer consists of approximately 75% PVA units and 25% PEG units on a weight basis. PVA-PEG graft co-polymer is primarily intended for use as a film coating on food supplement products. Specifically, the sponsor is requesting that the co-polymer be considered for use as a glazing agent, binder for tablets and stabilizer in food supplements at a level not to exceed 10% in the food supplement. The sponsor indicates that the final co-polymer formulation may contain 0.3 to 0.5% colloidal silica to improve the flow of the co-polymer in powder form.

2. Description

Graft copolymers are a form of copolymer where the side chains are structurally different from the main chain. PVA-PEG graft co-polymer is a synthetic branched graft co-polymer consisting of side chains of PVA on a main chain of PEG. The copolymer is made up of approximately 75% vinyl alcohol units (-CH_2CH_2(OH)-) and 25% ethylene glycol units (-CH_2CH_2O-). PVA-PEG graft co-polymer is manufactured by forming polyvinyl acetate side chains onto a PEG backbone that has an average molecular weight of 6,000 Daltons. The polyvinyl acetate side chains are then hydrolysed to form PVA side chains. The sponsor indicates that the copolymer has an average of 2 to 3 PVA side chains per polyethylene glycol backbone, and an average molecular weight between 40,000 and 50,000 Daltons.

Two CAS registry numbers are referenced for the polymer: 96734-39-3 and 121786-16-1. There is no definitive molecular formula for the PVA-PEG graft co-polymer. However, the following structural formula is representative of the copolymer.



PVA-PEG graft co-polymer is authorized for use in the preparation of pharmaceutical products in a number of countries and regions including Europe, Japan, and the USA. It is also permitted for use at levels up to 10% in the EU in food supplements (Food category 17.1) based on Commission Regulation (EU) No 685/2014.

3. Manufacturing process

PVA-PEG graft co-polymer is synthesized by means of a two-step reaction process. In the first step, a polymerization reaction occurs whereby PEG and vinyl acetate are reacted together in the presence of a polymerization initiator in methanol to form PEG-graft-poly(vinyl acetate) co-polymer. In the second step, the PEG-graft-poly(vinyl acetate) co-polymer is further reacted with sodium methoxide in methanol to form PVA-PEG graft co-polymer and methyl acetate. No additional catalysts are used. The polymer solution is then purified by steam distillation.

4. Chemical characterization

4.1 Composition

The co-polymer is characterized by an average molecular weight of 40,000 to 50,000 Daltons. The bulk material appears as a white to pale yellow free-flowing powder. The co-polymer is freely soluble in water, but is practically insoluble in undiluted ethanol, acetic acid, acetone, and chloroform. The co-polymer does, however, dissolve in dilute acids and dilute alkali hydroxides.

The sponsor provided data on the analysis of the co-polymer by means of infrared and nuclear magnetic resonance spectroscopic methods.

4.2 Impurities

The predominant impurities identified by the sponsor for the PVA-PEG graft-co-polymer are carry-over impurities from the starting materials, residual solvents, reaction by-products, and heavy metals. Table 1, below, summarizes the testing performed by the sponsor for select impurities on three lots of PVA-PEG graft co-polymer.

Table 1. Data from analysis of three lots of PVA-PEG graft co-polymer for certain impurities

Impurity	Residue Level		
	Lot 87194447G0	**40692124U0**	**30220936W0**
Ethylene glycol[1]	<50 mg/kg	<50 mg/kg	<50 mg/kg
Diethylene glycol[1]	<50 mg/kg	<50 mg/kg	<50 mg/kg
1,4-Dioxane	<10 mg/kg	<10 mg/kg	<10 mg/kg
Ethylene oxide	<0.2 mg/kg	<0.2 mg/kg	<0.2 mg/kg
Methanol	<10 mg/kg	<10 mg/kg	<10 mg/kg
Methyl acetate	<2 mg/kg	<2 mg/kg	<2 mg/kg
Heavy Metals (as Pb)	<20 mg/kg	<20 mg/kg	<20 mg/kg
Lead	<0.5 mg/kg	<0.5 mg/kg	<0.5 mg/kg
Vinyl acetate	<20 mg/kg	<20 mg/kg	<20 mg/kg
Acetic acid/Total acetate	0.65%	0.67%	0.65%

4.2.1 Ethylene oxide and 1,4-dioxane

In the first step of the manufacturing process for PVA-PEG graft co-polymer, PEG is reacted with vinyl acetate to form side chains of polyvinyl acetate on the PEG. Ethylene oxide and 1,4-dioxane, are known impurities in the PEG starting material. As shown in Table 1, the sponsor analysed three lots of PVA-PEG graft co-polymer for ethylene oxide and 1,4-dioxane, and found levels below 0.2 mg/kg and 10 mg/kg, respectively.

4.2.2 Ethylene glycol and diethylene glycol

Ethylene glycol and diethylene glycol are known impurities in the PEG starting material. They could also be present as breakdown products of the polymer over time. As shown in Table 1, the sponsor analysed three lots of PVA-PEG graft co-polymer for ethylene glycol and diethylene glycol, and determined that they were present at levels < 50 mg/kg.

Subsequent to the data provided in Table 1, the sponsor provided additional data indicating that levels of ethylene glycol and diethylene glycol higher than the levels of <50 mg/kg reported in Table 1 could be found in the PVA-PEG graft co-polymer. Batch data from 32 samples analysed between 2011 and 2014 indicated that 8 samples for ethylene glycol and 9 samples for diethylene glycol contained levels of ethylene glycol and/or diethylene glycol above 50 mg/kg. For the data above 50 mg/kg, the samples showed levels of ethylene glycol and diethylene glycol ranging from 51-130 mg/kg and 52-133 mg/kg, respectively.

The sponsor also submitted stability data on three batches of PVA-PEG graft co-polymer maintained for 3 years at a temperature of 30°C and 70% relative humidity, and three batches maintained for 4 years at a temperature of 30°C and 70% relative humidity. All six batches of the PVA-PEG graft co-polymer were analysed at the start of the stability trial and reported to contain <50 mg/kg ethylene glycol and diethylene glycol. The levels of diethylene glycol remained at <50 mg/kg throughout both the 3 year and 4 year stability studies. Levels of ethylene glycol, however, increased to levels above

[1] Additional data for ethylene glycol and diethylene glycol were also submitted that show residue levels above 50 mg/kg.

50 mg/kg in all 6 batches analysed in the 3 and 4 year studies by the conclusion of both studies. At the conclusion of the 3 year study, the levels of ethylene glycol ranged from 160-310 mg/kg. At the conclusion of the 4 year study, the levels of ethylene glycol ranged from 85-120 mg/kg.

As a result of the presence of ethylene glycol and diethylene glycol in PVA-PEG graft co-polymer at levels above the previously reported levels of < 50 mg/kg, the Committee decided to increase the specification limit for ethylene glycol and diethylene glycol above the limit of 50 mg/kg found in Commission Regulation (EU) No 685/2014 in order to reflect the levels found in products sold in commerce. Based on the ethylene glycol and diethylene glycol residue data included in the stability study data submitted by the sponsor, the Committee determined that a level of 400 mg/kg for ethylene glycol and diethylene glycol (singly or in combination) would cover combined levels of ethylene glycol and diethylene glycol in all batches of PVA-PEG graft co-polymer for which the sponsor submitted data.

4.2.3 Vinyl acetate

Vinyl acetate is one of the starting materials used to manufacture PVA-PEG graft co-polymer, and as a result, may remain as an impurity in the finished co-polymer. The sponsor analysed three lots of PVA-PEG graft co-polymer for the presence of vinyl acetate. The results are shown in Table 1.

4.2.4 Methanol

The sponsor indicates that both steps of the two step synthesis for PVA-PEG graft co-polymer employ methanol as a solvent. As such, the only residual solvent that would be expected is methanol. The data presented in Table 1, above, indicate that residual methanol in the three lots of PVA-PEG graft co-polymer tested were below a level of 10 mg/kg.

4.2.5 Acetic acid and methyl acetate

Acetic acid and methyl acetate are formed as by-products during the synthesis of PVA-PEG graft co-polymer. As shown in Table 1, levels of acetic acid in the three lots of the co-polymer tested ranged from 0.65-0.67%, and levels of vinyl acetate were below 20 mg/kg.

4.3 Analytical methods

The analytical methods that support the JECFA specifications are based on general tests in the FAO Combined Compendium of Specifications (FAO JECFA Monographs 1, vol. 4, 2006), methods provided directly by the sponsor, as well as those for the monograph Macrogol Poly(Vinyl alcohol) Grafted Copolymer in the Eighth Edition (through supplement 8.5) of the European Pharmacopoeia, and the monograph for Ethylene Glycol and Vinyl Alcohol Graft Copolymer in the United States Pharmacopeia/National Formulary (USP38/NF33). A comparison of the specifications for PVA-PEG graft co-copolymer as they appear in the European Pharmacopoeia, USP/NF, EU Commission Regulation No. 685/2014 and the recommendations of the sponsor appear, below, in Table 2.

Table 2. Comparison of Specifications

Specification/ Test	**European Pharmacopoeia Eighth Edition (Through Supplement 8.5) specifications for Macrogol Poly(Vinyl Alcohol) Grafted Copolymer**	**United States Pharmacopeia/ National Formulary (USP38/NF33) specifications for Ethylene Glycol and Vinyl Alcohol Graft Copolymer**	**European Union Specifications for E 1209 Polyvinyl Alcohol-Polyethylene glycol-graft-copolymer (COMMISSION REGULATION (EU) No 685/2014)**	**Sponsor Recommended Specifications**	**JECFA Specifications for PVA-PEG graft co-polymer**
IR Spectrum	Comparison with reference standard	Comparison with USP Reference Standard	Must comply	Must comply	Comparison with reference spectra
Film Formation	Transparent film is formed	N/A	N/A	N/A	Transparent film is formed
pH value	5.0 to 8.0	5.0 to 8.0	5.0-8.0	5.0 to 8.0	5.0-8.0
Ester value	10 to 75	10 to 75	10 to 75 mg/g KOH	10 to 75 mg/g KOH	10 to 75 mg/g KOH
Viscosity	<250 mPa-s,	25 to 250 mPa-s	50 to 250 mPa-s	50 to 250 mPa-s	50 to 250 mPa-s
Loss on drying	Max. 5%	NMT 5%	NMT 5%	NMT 5%	NMT 5%
Sulphated ash	Max. 3%	NMT 3%	NMT 2%	NMT 2%	NMT 2%
Vinyl acetate	NMT 100 mg/kg	NMT 100 mg/kg	NMT 20 mg/kg	NMT 20 mg/kg	NMT 20 mg/kg
Acetic acid/Total acetate	NMT 1.5%	NMT 1.5%	NMT 1.5%	NMT 1.5%	NMT 1.5%
Ethylene glycol and diethylene glycol	NMT 620 mg/kg ethylene glycol based on residual solvent limits; There is no specification for diethylene glycol.	NMT 620 mg/kg ethylene glycol based on residual solvent limits; There is no specification for diethylene glycol.	NMT 50 mg/kg for each individually	N/A	400 mg/kg (singly or in combination)
1,4-Dioxane	10 mg/kg	NMT 10 ppm dioxane	NMT 10 mg/kg	N/A	NMT 10 mg/kg
Ethylene oxide	1 mg/kg	NMT 1 mg/kg ethylene oxide	NMT 0.2 mg/kg	N/A	NMT 0.2 mg/kg

Specification/ Test	European Pharmacopoeia Eighth Edition (Through Supplement 8.5) specifications for Macrogol Poly(Vinyl Alcohol) Grafted Copolymer	United States Pharmacopeia/ National Formulary (USP38/NF33) specifications for Ethylene Glycol and Vinyl Alcohol Graft Copolymer	European Union Specifications for E 1209 Polyvinyl Alcohol-Polyethylene glycol-graft-copolymer (COMMISSION REGULATION (EU) No 685/2014)	Sponsor Recommended Specifications	JECFA Specifications for PVA-PEG graft co-polymer
Arsenic	N/A	N/A	NMT 3 mg/kg	N/A	N/A
Lead	N/A	N/A	NMT 1 mg/kg	NMT 1 mg/kg	NMT 1 mg/kg
Mercury	N/A	N/A	NMT 1 mg/kg	N/A	N/A
Cadmium	N/A	N/A	NMT 1 mg/kg	N/A	N/A
Residual Solvents - Methanol	N/A	N/A	N/A	N/A	N/A
Methyl acetate	N/A	N/A	N/A	N/A	N/A

N/A = Not applicable
NMT = not more than

The sponsor has not provided an analytical method for the direct determination of levels of PVA-PEG graft co-polymer when used as a film coating or binder in food tablets. They indicate that near infrared (NIR) or infrared (IR) methods may be used to quantify the co-polymer, but no methods or additional information was provided. The sponsor indicates that if the co-polymer is used as a film coating on food supplement tablets, then a weigh-by-difference method can be used to determine the amount of the co-polymer on the tablet. However, a weigh-by-difference method would require knowledge of the weight of the tablet prior to film coating.

5. Functional uses

5.1 Technological function

The sponsor is requesting that the co-polymer be considered for use as a binding agent (binder for tablets), glazing agent and stabilizer in food supplements. The predominant use in food supplements appears to be that of a glazing agent, or, more specifically, that of a film coating. The sponsor indicates that the co-polymer is intended for use in aqueous instant-release film coatings for food supplement products, however, they indicate that it can also be used for all applications in which a water-soluble flexible polymer is necessary. They indicate that film coating is the process by which a thin, polymer-based coating is applied to the surface of a food supplement tablet or capsule such that after evaporation of the water a clear, colourless flexible coating remains. They indicate that when used as a film coating, PVA-PEG graft co-polymer protects against unpleasant tastes or odours, improves appearance, makes the food supplements easier to swallow, and protects the active ingredients in the food supplement. Properties of the co-polymer that are beneficial to its use as a film coating include its low viscosity in aqueous solutions, its high flexibility and elasticity,

its rapid dissolution in acidic, neutral, and aqueous media, its ability to reduce the surface tension of water (and thus easier to spray onto food supplements), and its lack of tackiness when formed as a film (which makes it easier to print on). It also has the benefit of being able to form flexible films without the need for an additional plasticizer.

The sponsor also indicates that PVA-PEG graft co-polymer may be used as a binder in rapidly dispersible/soluble granules or tablets, and as a suspension and emulsion stabilizer and protective colloid.

5.2 Food categories and use levels

The sponsor states that film coating formulations containing PVA-PEG graft co-polymer for food supplements are typically applied at a level of 2 to 4 mg/cm^2 on the food supplement. On a dry weight basis, the co-polymer can comprise from 60-100% of the film coating formulation. In total, the sponsor indicates that the PVA-PEG graft co-polymer would provide no more than a 5% weight gain to the overall weight of the capsule. Thus, a use level of 5% would be appropriate for use of the PVA-PEG graft co-polymer as a film coating on food supplements.

The sponsor also indicates that for uses other than as a film coating agent (e.g., binder, stabilizer) a use level up to 10% of the weight of the food supplement would typically be needed.

Table 3. General Standard for Food Additives (GSFA) food category and use levels for PVA-PEG graft co-polymer

GSFA Food Category	Use	Use Level (mg/kg)
13.6 (Food supplements)	Glazing agent (film coating)	5% (50,000 mg/kg)
13.6 (Food supplements)	Binder, Stabilizer	10% (100,000 mg/kg)

6. Reactions and Fate in Food

The stability of PVA-PEG graft co-polymer was evaluated under intermediate storage condition (30°C and 70% relative humidity) for thirty-six months and accelerated storage conditions (40°C and 75% relative humidity) for six months. The testing was carried out in accordance with the International Conference on Harmonization (ICH) guidelines for stability testing of new drug substances and products (ICH, 2003). The stability data for three lots of the co-polymer provided by the sponsor indicate that the products were within the limits of specifications for the co-polymer.

The sponsor indicated that reactions between the PVA-PEG co-polymer and the active ingredients of food supplements are not expected. They support this statement by noting the absence of such reactions from the world-wide use of the co-polymer as a film-coating agent for pharmaceutical products. In addition, as the co-polymer is readily soluble in water as well as acids and bases, it should not interfere with the release of the food supplement ingredients.

The sponsor does note, however, that a number of potential reactions have been described for the individual components of the co-polymer, PVA and PEG, in the Handbook of Pharmaceutical Excipients (Rowe et al., 2009a,b). For example, as PVA and PEG possess terminal and secondary hydroxyl groups, respectively, these are susceptible to esterification or etherification reactions (Rowe et al., 2009a,b). It is also indicated that liquid and solid PEG grades may be incompatible with some colouring agents (Rowe et al., 2009a). In addition, it is noted that PEG can exhibit oxidizing activity

due to the presence of peroxide impurities and secondary products formed by autoxidation (Rowe et al., 2009a). Finally, it is noted that PEG can migrate from tablet film coatings leading to interaction with the core components (Rowe et al., 2009a). The sponsor notes, however, that such reactions are not expected with PVA-PEG graft co-polymer as the plasticizer is covalently bound in the co-polymer, and cannot migrate to the tablet core.

7. References

EC. Regulation (EU) No 685/2014 of 20 June 2014 amending Annex II to Regulation (EC) No 1333/2008 of the European Parliament and of the Council and the Annex to Commission Regulation (EU) No 231/2012 as regards polyvinyl alcohol- polyethylene glycol-graft-co-polymer in solid food supplements.

EFSA. ANS Panel (EFSA Panel on Food Additives and Nutrient Sources added to Food). Scientific Opinion on the safety of polyvinyl alcohol-polyethylene glycol-graft-co-polymer as a food additive. EFSA Journal 2013;11(8):3303. 30 pp doi:10.2903/j.efsa.2013.3303

ICH. Stability Testing of New Drug Substances and Products: Q1A(R2). Current Step 4 Version Dated 6 February 2003. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceutical for Human Use (ICH). (ICH Harmonised Tripartite Guideline), 2003. Available at: http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Quality/Q1A_R2/Step4/Q1A_R2Guideline.pdf

Ph. Eur. Macrogol poly(vinyl alcohol) grafted copolymer. In: European Pharmacopoeia. 8th ed. Strasbourg, France: Directorate for the Quality of Medicines of the Ph. Eur., Strasbourg, France., pp. 2660-2662, 2014.

Rowe RC, Shesky PJ, Quinn ME, eds. Polyethylene glycol. In: Handbook of Pharmaceutical Excipients. 6th ed. London, Engl.: Pharmaceutical Press / Washington (DC): American Pharmaceutical Association (APhA), pp. 517-522, 2009a.

Rowe RC, Shesky PJ, Quinn ME, eds. Polyvinyl alcohol. In: Handbook of Pharmaceutical Excipients. 6th ed. London, Engl.: Pharmaceutical Press / Washington (DC): American Pharmaceutical Association (APhA), pp. 564-565, 2009b.

USP/NF monograph for Ethylene Glycol and Vinyl Alcohol Graft Copolymer. In: United States Pharmacopeia 38/National Formulary 33. United State Pharmacopeial Convention Inc., Rockville, MD, pp. 6662-6664, 2015.