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Characterisation and toxicological assessment of Neutral Methacrylate Copolymer for GRAS evaluation

Johanna Eisele [a,1], Geoff Haynes [b,2], Knut Kreuzer [a,3], Tiana Rosamilia [c,*]

[a] Evonik Industries AG, Kirschenallee, 64293 Darmstadt, Federal Republic of Germany
[b] Haynes Safety Services Ltd., Oakridge, Quarry Lane, Gorsley, Ross-on-Wye, Herefordshire HR9 7SJ, England, United Kingdom
[c] Evonik Corporation, 299 Jefferson Rd., Parsippany, NJ 07054, United States

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ABSTRACT

Neutral Methacrylate Copolymer is a fully polymerised copolymer used in the pharmaceutical industry to permit pH-independent delayed release of active ingredients from oral dosage forms. This function has potential use with food supplements and this article describes available information on the safety of the substance.

Oral administration of radiolabelled copolymer to rats resulted in the detection of chemically unchanged copolymer in the faeces, with negligible absorption. Safety studies revealed no adverse toxicity following repeated administration at doses of up to 2000 mg/kg bw/d in a sub-chronic study in rats or 250 mg/kg bw/d in a sub-chronic study in dogs. No reproductive toxicity occurred at up to 2000 mg/kg bw/d in rats or rabbits. The substance shows no evidence of genotoxicity, has low acute toxicity and no irritation or sensitisation potential.

An ADI value of 20 mg/kg bw was concluded from two alternative approaches. Daily exposure from use in dietary supplements is estimated as up to 10.0 mg/kg bw in adults and 13.3 mg/kg bw in children. There would therefore appear to be no safety concerns under the intended conditions of use. The information provided is intended to support an evaluation that the substance may be "generally recognized as safe" (GRAS).

1. Introduction

The purpose of this article is to provide a summary of the production, identity, physicochemical characteristics and toxicological properties of Neutral Methacrylate Copolymer (NMC). Until recently, use of the substance has been limited to pharmaceutical preparations. Use is likely to expand to dietary supplements and, with due consideration to this increase, available information should be made generally available to those interested in the safety of food additives. The information presented in this article, in particular the toxicological studies, both support the safety of NMC for use as a coating for dietary supplements and are intended to support an evaluation that the substance may be "generally recognised as safe" (GRAS).

1.1. Historical perspective

NMC has been employed since its introduction in 1972 as an excipient in preparations for oral pharmaceutical dosage forms as a glazing/coating agent to permit the pH-independent delayed release of active ingredients from oral dosage forms. In their publication of 1974, Lehmann and Dreher mentioned the substance as an

Abbreviations: BCA, bicinchoninic acid; bw, body weight; CAS, Chemical Abstract Service; DMEM, Dulbecco's Modified Eagle's Medium; DMF, drug master file; DMSO, dimethyl sulphoxide; DNFCS, Dutch National Food Consumption Survey; EA, ethyl acrylate; EC, European Council; EFSA, European Food Safety Authority; GLP, Good Laboratory Practice; GPC, gel permeation chromatography; GRAS, generally recognised as safe; ICH, International Conference on Harmonisation of technical requirements for registration of pharmaceuticals for human use; INCI, International Nomenclature for Cosmetic Ingredients; IUPAC, International Union of Pure and Applied Chemistry; JPE, Japanese Pharmaceutical Excipients; LD50, median lethal dose; MMA, methyl methacrylate; Mn, average molecular weight by number; MNPCE, micronucleated polychromatic erythrocytes; MOS, margin of safety; Mw, average molecular weight by weight; NOAEL, no observed adverse effect level; NMT, not more than; OECD, Organisation for Economic Co-operation and Development; PCE, polychromatic erythrocytes; Ph. Eur., European Pharmacopoeia; RIVM, Rijksinstituut voor Volksgezondheid en Milieu; SCF, Scientific Committee on Food; SEM, scanning electron microscope; TDI, total daily intake; TK, thymidine kinase locus; UK, United Kingdom; US, United States; USA, United States of America; USP/NF, United States Pharmacopoeia/National Formulary.

* Corresponding author. Fax: +1 973 929 8040.
E-mail addresses: Johanna.Eisele@Evonik.com (J. Eisele), geoff.haynes@breatheconnect.com (G. Haynes), Knut.Kreuzer@Evonik.com (K. Kreuzer), Tiana.Rosamilia@Evonik.com (T. Rosamilia).
[1] Fax: +49 6151 18 84 4763.
[2] Fax: +44 1989 720103.
[3] Fax: +49 6151 18 84 4421.

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excipient for delayed drug release. Sustained-release formulations allow the continuous dissolution of a nutrient over a defined time and this functionality is obtained via the permeability of the coating in aqueous media (McGinity and Felton, 2008). In 1976 a Drug Master File (DMF) describing the substance was submitted to the US FDA, the number 2822 was assigned. The DMF refers to the same polymer produced with two different emulsifiers (0.7% Macrogol Stearyl Ether (20) and 1.5% Nonoxynol 100). NMC conforms to the substance produced with Macrogol Stearyl Ether as emulsifier. The US FDA assigned in their Substance Registration System the UNique Ingredient Identifier (UNII) code XRK36F13ZZ for the copolymer with Macrogol Stearyl Ether as emulsifier and P2OM2Q86BI for the copolymer with Nonoxynol 100 as the emulsifier (FDA, 2013a). The UNII code P2OM2Q86BI is also listed in the US FDA IIG (Inactive Ingredient Database; FDA, 2013b). Specifications are described in the monographs of a number of pharmacopoeias including the United States Pharmacopoeia/National Formulary (“Ethyl Acrylate and Methyl Methacrylate Copolymer Dispersion – NF”; USP 2013), the European Pharmacopoeia (“Polyacrylate Dispersion 30 Per Cent – Ph. Eur.”; EDQM, 2013) and the Japanese Pharmaceutical Excipients compendium (“Ethyl Acrylate and Methyl Methacrylate Copolymer Dispersion –JPE”; JPEC, 2004).

Many dietary supplements have the same requirements on functional food additives as oral pharmaceuticals on functional excipients. Considering this, NMC has been proposed for use as a glazing agent/coating agent in solid food supplements as defined by the European Commission in the European Directive 2002/46/EC (2002) and in solid foods for special medical purposes as defined by the European Commission in the European Directive 1999/21/EC (1999). A submission has been made to the European Food Standards Agency (EFSA) for these uses and a positive scientific opinion was published in July 2010 (EFSA, 2010a) which concluded that, based on a margin of safety (MOS) of at least 43 for adults and at least 63 for children, the use of NMC as a glazing agent/coating agent in solid food supplements for sustained release formulations is not a safety concern at the proposed use levels.

2. Identity and properties

NMC is a fully polymerised copolymer of methyl methacrylate and ethyl acrylate. The quantitative composition of the polymer is described as poly(ethyl acrylate-co-methylmethacrylate) 2:1 under IUPAC nomenclature, this description provides an indication of the ratio of the two monomers in the copolymer. The representative chemical formula is described in Fig. 1. The CAS Registry Number is 9010-88-2.

The weight average molar mass (Mw) is approximately 600,000 g/mol and the molecular number (Mn) is approximately 220,000 g/mol. This data has been obtained by GPC (on the basis of ISO 13885-1). The molecular weight distribution has been determined by size exclusion chromatography (Adler et al., 2005) and the distribution is illustrated as two overlays of a total 6 samples (see Fig. 2). Earlier viscosimetric measurements, as done in the 1960’s, gave a Mw of 800,000 g/mol for NMC, but this value may not be correct in the light of current analytical methods.

Details of the low molecular weight fraction are contained in Table 1.

In pharmaceutical use the chemically identical polymer with user-optimized specifications is named Polyacrylate Dispersion 30 Per Cent (Ph. Eur.). Its INCI name is Acrylates Copolymer. It is made commercially available by Evonik Industries AG as 30% aqueous polymeric dispersions (EUDRAGIT® NM 30 D, EUDRAGIT® NE 30 D) and a 40% aqueous polymeric dispersion (EUDRAGIT® NE 40 D). In order to justify the reference of Neutral Methacrylic Copolymer to data obtained for the polymer with Nonoxynol as the emulsifier (EUDRAGIT® NE 30 D), a spectroscopic comparison was performed. Freeze-dried polymers with either Nonoxynol or Macrogol as the emulsifier were investigated by ^{1}H and ^{13}C NMR-measurements (Nuclear magnetic resonance) as well as by Fourier transform infrared (FTIR) spectroscopy. Measurements revealed the two polymer types to be effectively the same.

The production process follows the requirements of the joint International Pharmaceutical Excipients Council’s and the Pharmaceutical Quality Group’s “Good Manufacturing Practices Guide for Pharmaceutical Excipients” of 2006 (IPEC/PQG, 2006) and USP/NF General Chapter <1078> to meet the quality demands of the pharmaceutical industry (USP, 2013).

2.1. Manufacturing process

The copolymer is produced using a process of emulsion polymerisation in which there is a redox initiated polymerisation of the monomers ethyl acrylate and methyl methacrylate by using a free radical donor redox initiator system. Polyethylene glycol monostearyl ether is used as an emulsifier in the process. An alkyl mercaptane is used as a chain modifying agent. At the end of the polymerisation an emulsifier is added to reduce foaming. Residual monomers and excess water are removed by water vapor distillation. The dispersion is cooled to room temperature and the pH of the reaction mixture is adjusted with sodium hydroxide. Sodium hypochlorite is added to prevent microbial contamination during the filtration and filling process.

In a coating of a tablet or pellet NMC is sprayed on the tablet or pellet. Film formation takes place through evaporation of the water so that the polymer particles move closer and closer until they enter into contact and form a packed film. Fig. 3 shows a scanning electron microscope (SEM) micrograph of a tablet coated with NMC.

2.2. Physicochemical properties

The commercial dispersion of NMC is stable for at least 24 months at ambient temperatures. The copolymer shows high thermal and chemical stability. Pan coating and fluid-bed processing are the conventional methods for coating solid dosage forms such as tablets or smaller particles such as pellets and granules. When processing the copolymer in this way, the process temperature is in the range of 20–25 °C. The copolymer is completely stable at these processing temperatures, showing thermal stability up to 300 °C at which depolymerisation may occur.

In the commercial form the copolymer appears as milky-white liquid of low viscosity with a faint characteristic odour. The aqueous dispersion is miscible with water in any proportion, the milky-white appearance being retained. When dried, the copolymer forms a film.

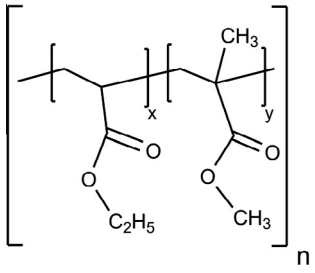

Fig. 1. Representative chemical formula of Neutral Methacrylate Copolymer.