Table of Contents

INTRODUCTION ............................................. 4
CHEMISTRY .................................................. 5
  Origin
  Manufacturing
  Grades and Types
PHYSICOCHEMICAL PROPERTIES ....................... 6
  Product Specifications
  Morphology
  Moisture Absorption
  Thermal Properties
    Glass Transition Temperature
    Thermal Decomposition Temperature
    Melt Viscosity
    Melt Viscosity with Various Plasticizers
  Viscosity in Various Solvents
  Solubility at Various pH
  Film Strength
APPLICATIONS ............................................. 12
  Solid Dispersion for Bioavailability Enhancement
  Enteric Coating
INCOMPATIBILITIES ..................................... 15
STABILITY AND STORAGE CONDITIONS .................. 15
PACKAGING AND SHIPPING ............................... 15
REGULATORY STATUS ................................. 15
TOXICOLOGY ............................................. 15
REFERENCES ............................................. 15
Introduction

AquaSolve™ hydroxypropylmethylcellulose acetate succinate (HPMCAS; known as hypromellose acetate succinate in pharmaceutical applications) is a mixture of acetic acid and monosuccinic acid esters of hydroxypropylmethyl cellulose in the form of a white to off-white powder or granules. It has a faint acetic acid-like odor and a barely detectable taste. AquaSolve HPMCAS is available in several grades varying in extent of substitution of acetyl and succinoyl groups and in particle size (fine or granular).

AquaSolve HPMCAS can be used as a solid-dispersion carrier for bioavailability enhancement of poorly soluble compounds. It is insoluble in gastric fluid, but will swell and dissolve rapidly in the upper small intestine. AquaSolve HPMCAS is commonly used as an enteric film-coating agent for tablets, capsules and granules. For aqueous film-coating purposes, a dispersion of HPMCAS fine powder and plasticizer (such as triethyl citrate) in water is commonly used. AquaSolve HPMCAS is also used in preparation of sustained drug-release formulations. The release rate of the model drug from the matrix is pH dependent. Other formulation options include neutralized-solution/organic-solvent applications and dry-powder coating.

AquaSolve HPMCAS has the following functions and properties:
- It is practically insoluble in water, ethanol and hexane.
- It may have a faint acetic acid-like odor.
- It is tasteless.
- It is physiologically inert.
- It is a preferred solid-dispersion carrier for bioavailability enhancement.
- It is an enteric coating polymer.

These properties and functions make it suitable for use in many pharmaceutical applications. The polymer is available in three grades: L, M and H, based on the content of acetyl and succinoyl groups (wt%) in the HPMCAS molecule. Each grade is available in two different particle sizes, F (fine) and G (granular).

This handbook describes basic chemical and physical properties of AquaSolve HPMCAS. The range of types produced and the typical uses for this versatile cellulosic enteric polymer are also discussed.
Figure 1 shows the structure of the HPMCAS molecule; it is visualized as a polymer chain composed of 2-hydroxypropoxy groups (-OCH₂CH(CH₃)OH), methoxy groups (-OCH₃), acetyl groups (-COCH₃), and succinoyl groups (-COCH₂CH₂COOH).

CASRN: 7138-97-1
CAS Name: Cellulose, 2-hydroxypropyl methyl ether, acetate hydrogen butanedioate

Figure 1 – Structure of hydroxypropylmethylcellulose acetate succinate

Manufacturing
Acetic anhydride and succinic anhydride are reacted with hydroxypropylmethylcellulose (HPMC) under specifically controlled conditions to produce AquaSolve HPMCAS. The process begins with cellulose, a polymer chain composed of repeating β-1,4-anhydroglucose units. Each anhydroglucose unit contains three hydroxyl groups. The hydroxyl groups of HPMC used to make HPMCAS are substituted with specific levels of methoxyl and hydroxypropoxy groups. The degree of substitution (DS) of methoxyl on HPMC ranges from 1.78 to 2.02 while the molar substitution of hydroxypropoxy is 0.23 to 0.41. The methoxyl DS influences the amount of free hydroxyl groups available for further substitution. Because the hydroxypropoxy group by definition contains a hydroxyl substitution, the level of hydroxypropoxy substitution does not change the overall number of hydroxyl groups available for further substitution. When HPMC is reacted with defined quantities and ratios of acetic anhydride and succinic anhydride, HPMCAS is produced, containing various levels of acetyl and succinoyl esters.

Grades and Types
AquaSolve HPMCAS is produced in three substitution grades: L, M and H. The three grades are insoluble in acidic aqueous solutions. All three grades are soluble in dilute caustic solution, and to various degrees in acetone and methanol. Each grade is available in fine (F) and granular (G) particle sizes. The range of grades is listed in Table 1, according to the content of acetyl groups. The contents of the other major substituent groups are also listed in the table. Unless otherwise noted, all percentages in this text are percentages by weight.

Table 1 – AquaSolve™ HPMCAS grades

<table>
<thead>
<tr>
<th>Grade</th>
<th>Acetyl Content</th>
<th>Succinoyl Content</th>
<th>Methoxyl Content</th>
<th>Hydroxypropoxy Content</th>
</tr>
</thead>
<tbody>
<tr>
<td>L</td>
<td>5–9%</td>
<td>14–18%</td>
<td>20–24%</td>
<td>5–9%</td>
</tr>
<tr>
<td>M</td>
<td>7–11%</td>
<td>10–14%</td>
<td>21–25%</td>
<td>5–9%</td>
</tr>
<tr>
<td>H</td>
<td>10–14%</td>
<td>4–8%</td>
<td>22–26%</td>
<td>6–10%</td>
</tr>
</tbody>
</table>

Figure 2 shows the available grades of AquaSolve
Figure 2 – Available grades of AquaSolve™ HPMCAS

Table 2 – Product specifications

<table>
<thead>
<tr>
<th>AquaSolve™ HPMCAS</th>
<th>LF and LG</th>
<th>MF and MG</th>
<th>HF and HG</th>
</tr>
</thead>
<tbody>
<tr>
<td>Appearance</td>
<td>White to off-white powder (F) or granules (G)</td>
<td>Conforms to U.S. National Formulary and Japanese Pharmacopoeia monographs</td>
<td></td>
</tr>
<tr>
<td>Viscosity</td>
<td>2.4–3.6 mPa•s</td>
<td>≤ 5%</td>
<td></td>
</tr>
<tr>
<td>Loss on Drying</td>
<td>≤ 5%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Residue on Ignition</td>
<td>≤ 0.20%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heavy Metals</td>
<td>&lt; 10 ppm</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arsenic</td>
<td>≤ 2 ppm</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Limit of Free Succinic and Acetic Acids</td>
<td>≤ 1.0%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acetyl Content</td>
<td>5–9%</td>
<td>7–11%</td>
<td>10–14%</td>
</tr>
<tr>
<td>Succinoyl Content</td>
<td>14–18%</td>
<td>10–14%</td>
<td>4–8%</td>
</tr>
<tr>
<td>Methoxyl Content</td>
<td>20–24%</td>
<td>21–25%</td>
<td>22–26%</td>
</tr>
<tr>
<td>Hydroxypropoxy Content</td>
<td>5–9%</td>
<td>5–9%</td>
<td>6–10%</td>
</tr>
<tr>
<td>Average Particle Size (Laser Diffraction) F Types</td>
<td>≤ 10 microns</td>
<td></td>
<td></td>
</tr>
<tr>
<td>D90 (Laser Diffraction) F Types</td>
<td>≤ 20 microns</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

1 Measured for a 2% solution at 20°C.


Ashland can tailor certain chemical and physical properties of AquaSolve HPMCAS to meet users’ unique requirements. Users are encouraged to discuss their needs with their Ashland technical representative, or to call the toll-free number shown on the back cover of this booklet for product information.
Morphology
The fine grind grades of AquaSolve HPMCAS are rounded to elongated particles ranging from approximately 0.50 to 1.50 microns in diameter mixed with elongated to rounded fairly dense agglomerates ranging up to around 10.0 microns in diameter. The coarse grind grades of AquaSolve HPMCAS consist of large, fairly dense, rounded and slightly elongated agglomerates ranging up to approximately 1.60 mm in length. The fine elongated to round particles that form the agglomerates range up to around 30.0 microns in length. Representative samples of AquaSolve MF and MG HPMCAS are shown in Figures 3 and 4.

Moisture Absorption
AquaSolve HPMCAS absorbs moisture from the air. The amount absorbed and the rate of absorption depend on the initial moisture content and on the relative humidity and temperature of the surrounding air. Figure 5 shows the effect of relative humidity on equilibrium moisture content of three grades of AquaSolve HPMCAS.
**Thermal Properties**

**Glass Transition Temperature**

Glass transition temperatures ($T_g$) of polymers were tested using differential scanning calorimetry (DSC) under a nitrogen purge with a TA Instruments DSC2000 calorimeter on 5 mg samples. Each sample was heated at a rate of 20°C/minute from −20°C to 190°C and then cooled at the same rate back to −20°C. After cooling, samples were held isothermal for 5 minutes and then heated again at the same rate to 195°C. The glass transition temperature was identified as the half-height midpoint for the reheat data cycle. All three grades of HPMCAS have a $T_g$ near 120°C (Figure 6 and Table 3). Glass transition temperature helps to guide the lower end of hot-melt extrusion processing temperature. Typically, hot-melt extrusion is processed about 20–40°C above $T_g$.

**Figure 6 – Glass transition temperatures for each grade of AquaSolve™ HPMCAS**

**Thermal Decomposition Temperature**

Thermal decomposition temperature ($T_d$) was measured by thermogravimetric analysis (TGA). TGA was performed on 10 mg samples in a TA Instruments TGA Q5000IR® thermogravimetric analyzer under N2 atmosphere. Nitrogen flow rate was 25 ml/min at normal air pressure with a heating rate of 10°C/min. Samples were heated to above 800°C until 5% weight loss, excluding moisture loss. All three grades of AquaSolve HPMCAS had decomposition temperatures in the range of 258 to 276°C (Figure 7 and Table 3). Thermal decomposition temperature defines the higher end of the extrusion temperature range.

**Figure 7 – Thermal decomposition temperatures for each grade of AquaSolve™ HPMCAS**

**Table 3 – Glass transition and thermal decomposition temperatures of AquaSolve™ HPMCAS**

<table>
<thead>
<tr>
<th></th>
<th>L Grade</th>
<th>M Grade</th>
<th>H Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>$T_g$</td>
<td>119</td>
<td>120</td>
<td>122</td>
</tr>
<tr>
<td>$T_d$</td>
<td>258</td>
<td>267</td>
<td>276</td>
</tr>
</tbody>
</table>

**Melt Viscosity**

Melt viscosity information can help to identify the hot-melt extrusion processing temperature window. The influence of shear frequency (shear rate; see Figure 8) and temperature (see Figure 9) on melt viscosity were studied with a TA Instruments AR G2 stress-controlled rotational rheometer, with a 25 mm parallel-plate geometry. The isothermal frequency sweep test was conducted at 170°C with a frequency range from 0.1 rad/s to 600 rad/s and a strain in the linear viscoelastic region of the sample. All three grades of AquaSolve HPMCAS show shear thinning behavior at 170°C.
Figure 8 – Influence of shear frequency on melt viscosity of AquaSolve™ HPMCAS at 170°C

The temperature-sweep test was performed from 150°C to 200°C with a heating rate of 2°C/min. The measurement frequency was set at 6.28 rad/s and the strain was within the linear viscoelastic region of each sample. All grades of AquaSolve HPMCAS had melt viscosities below 100,000 Pa·s at these temperatures, which is the generally accepted upper viscosity limit for hot-melt extrusion. Viscosities of all three grades decreased with increasing temperature from 150°C to 200°C. The melt viscosity of the H grade is significantly lower compared with the M and L grades, especially at high temperatures.

Melt Viscosity with Various Plasticizers
Polymer and plasticizer mixtures were prepared by spray drying. Melt viscosity was evaluated using the same conditions as for the pure polymer. Results are shown in Figures 10 to 12 for each grade of AquaSolve HPMCAS. All plasticizers effectively reduced the melt viscosity to below 100,000 Pa·s, making extrusion possible at lower temperatures (around 120°C) to improve processability.

Figure 10 – Melt viscosity of AquaSolve™ L HPMCAS with various plasticizers at 10%
Viscosity in Various Solvents

A lower solution viscosity is advantageous for spray drying and coating. The typical concentration of total solids for spray drying is less than 10%, and concentrations of 3% to 5% are common. For film coating, polymer concentration is generally less than 10% in solution. The viscosity of solutions of each grade of AquaSolve HPMCAS in various solvents was measured using a Brookfield viscometer. Results are shown in Figures 13 through 15. At 10% solids content, a viscosity less than 300 mPa·s indicates good processability.

Figure 13 – Viscosity of AquaSolve L HPMCAS at 20°C in various solvents

Figure 14 – Viscosity of AquaSolve M HPMCAS at 20°C in various solvents
Solubility at Various pH
Polymer solubility at various pH was evaluated by disintegration of films in phosphate buffer solutions. Films were cast with acetone as the solvent to a thickness of 90 μm and cut into squares of 1.3 cm. Disintegration time was measured using a USP disintegration apparatus at 37°C following general USP disintegration guidelines. Results varied by grade and pH, as shown in Figure 16.

Film Strength
The films prepared for the dissolution testing were also used for film tensile strength evaluations. Films were cast to a thickness of 90 μm. An Instron Universal Tensile tester was used to perform the evaluations. Results are described in Table 4. Aquasolve L, M, and H grades of HPMCAS have similar film characteristics.

Table 4 – Film strength results

<table>
<thead>
<tr>
<th>Grade of Aquasolve™ HPMCAS</th>
<th>Elongation (%)</th>
<th>Modulus (MPa)</th>
<th>Yield Stress (MPa)</th>
</tr>
</thead>
<tbody>
<tr>
<td>L</td>
<td>11</td>
<td>1574</td>
<td>35</td>
</tr>
<tr>
<td>M</td>
<td>19</td>
<td>1523</td>
<td>37</td>
</tr>
<tr>
<td>H</td>
<td>16</td>
<td>1494</td>
<td>40</td>
</tr>
</tbody>
</table>
HPCMCAS has been used as an enteric film-coating polymer for tablets and also for capsules. Its effectiveness as a solid-dispersion carrier for bioavailability enhancement has attracted the most attention in recent years. Numerous publications have indicated that HPCMCAS is able to initiate and maintain supersaturation for drugs with a wide variety of structures and physical properties, and the efficacy advantage of HPCMCAS is primarily due to the polymer’s superior ability as a precipitation inhibitor via the formation of colloidal species in aqueous media.1,2

Solid Dispersion for Bioavailability Enhancement

Acetyl and succinyl substitution levels have a significant impact on the performance of HPCMCAS as an amorphous solid-dispersion carrier. This effect is demonstrated in a case study in which the dissolution performance of solid dispersions prepared by spray drying using AquaSolve HPCMCAS L, M and H grades and the poorly soluble compounds ezetimibe (EZE), itraconazole (ITZ) and felodipine (FEL) was evaluated. The acetyl to succinyl ratios of the AquaSolve L, M and H HPCMCAS grades were 0.48, 0.87 and 1.8, respectively.

Spray-drying solutions were prepared by dissolving model compound and polymer into 2:1 (w/w) dichloromethane:methanol solution at 5% solids. Spray drying was performed on a GEA SD Micro* Spray-Dryer. The feed material was atomized using a 0.5 mm two-fluid Schlick nozzle targeting an inlet temperature of 85°C, a process gas flow of 25 kg/hr, an atomizing gas pressure of 0.5 bar, and an atomizing-gas flow rate of 1.5 kg/hr. The liquid-feed rate was adjusted to maintain an outlet gas temperature of 55°C. After spray drying, the spray-dried dispersions were vacuum dried for 48 hours at 40°C under −25 in. Hg reduced pressure. The spray-dried powders were evaluated for the amorphous characteristics of the samples and the dissolution performance. All spray-dried solid dispersions were characterized as amorphous by X-ray powder diffraction (XRPD) performed on a Bruker D8 Focus diffractometer, using a copper tube element and a PSD LynxEye* detector.

Dissolution experiments were performed using a Pion μDISS Profiler* dissolution apparatus. Spray-dried samples were added to 20 ml of fasted-state simulated intestinal fluid (FaSSIF) maintained at 37°C under a constant stirring speed of 300 rpm. A 2.0 mg model drug equivalent of each spray-dried powder was added to each vial and drug concentration was measured by in situ fiber optic probes at various time points. For the solid dispersions of all three model compounds, L grades consistently gave the fastest initial dissolution (Figures 17 through 19). The ability of the polymer to maintain supersaturation was highly dependent on the interaction between model drug and polymer.

Figures 17 through 19 show the relative performance of AquaSolve HPCMCAS with different substitution levels on solubilization enhancement of model drugs with varying solubility.

Figure 17 – Kinetic solubility results for spray-dried dispersions produced with itraconazole (ITZ) and each grade of AquaSolve™ HPCMCAS at 25% drug load

Applications
Figure 18 – Kinetic solubility results for spray-dried dispersions produced with ezetimibe (EZE) and each grade of AquaSolve™ HPMCAS at 50% drug load

As indicated in Figure 17, the itraconazole solid dispersion had a greater area under the dissolution curve (AUC) when formulated with AquaSolve L and M grades of HPMCAS. Itraconazole is a weakly basic compound that can form ionic interactions with the succinoyl groups of HPMCAS. The L and M grades have more readily available succinoyl groups and rendered solid dispersions with better dissolution performance. Both ezetimibe (weak acid) and felodipine (neutral) showed low AUCs with L grade solid dispersions and higher AUC in M- and H-grade solid dispersions (Figures 18 and 19). For both compounds, M-grade solid dispersions performed similarly with H-grade solid dispersions. AquaSolve M and H HPMCAS are more hydrophobic than L grade, as indicated by their higher acetyl to succinoyl ratios, and these two grades therefore have stronger intermolecular interactions with hydrophobic ezetimibe and felodipine and were able to maintain supersaturation for prolonged periods.

It can be concluded from this case study that for basic compounds, like itraconazole, the L grade with more succinoyl groups can form ionic interactions and result in solid dispersions with better dissolution performance. For hydrophobic compounds such as ezetimibe and felodipine that are non-ionizable or acidic, the more hydrophobic H and M grades offer better performance due to their strong interactions with the compounds. In addition, the dissolution rate of the polymers has significant impact on the dissolution rate of the solid dispersions.

**Enteric Coating**

This case study was performed on tablets containing omeprazole as the model drug. Omeprazole is a proton-pump inhibitor that is unstable in acidic conditions, making an enteric coating necessary. An enteric coating dispersion formulation was prepared using a neutralization method by adding basic agents. The coating formulations are listed in Table 5 and were prepared as follows: triethyl citrate and sodium lauryl sulfate were added to water (at ambient conditions) and stirred for 5 min. AquaSolve HPMCAS and talc were added and stirred until uniformly distributed. Finally, monoethanolamine was added to the dispersion, pH was adjusted to pH 8 (target pH 7–9) with ammonium hydroxide and the mixture was stirred for 3 h at ambient conditions until no HPMCAS particles were left. The final step was filtration with a 20 mesh sieve. Alternatively, a 20 mesh screen can be placed at the end of the inlet tubing. The dispersion was gently stirred during the entire coating process to prevent the precipitation of talc.
Table 5 – Omeprazole tablet coating formulations

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Percent by Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>HPMCAS (L, M or H)</td>
<td>58.1</td>
</tr>
<tr>
<td>Monoethanolamine</td>
<td>3.4</td>
</tr>
<tr>
<td>Triethyl citrate</td>
<td>14.8</td>
</tr>
<tr>
<td>Sodium lauryl sulfate</td>
<td>1.6</td>
</tr>
<tr>
<td>Talc</td>
<td>20.0</td>
</tr>
<tr>
<td>Ammonium hydroxide</td>
<td>~2.1</td>
</tr>
</tbody>
</table>

The formulations were coated on 300 mg tablets containing a 20 mg dose of omeprazole, using the parameters listed in Table 6.

Table 6 – Omeprazole tablet coating parameters

<table>
<thead>
<tr>
<th>Parameter</th>
<th>O’Hara LabCoat II</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pan size</td>
<td>15 inch</td>
</tr>
<tr>
<td>Gun</td>
<td>Schlick 1.2 mm</td>
</tr>
<tr>
<td>Pan load (kg)</td>
<td>3</td>
</tr>
<tr>
<td>Pan speed (rpm)</td>
<td>14</td>
</tr>
<tr>
<td>Bed temperature (°C)</td>
<td>45–50</td>
</tr>
<tr>
<td>Spray rate (g/min)</td>
<td>20</td>
</tr>
<tr>
<td>Inlet temperature (°C)</td>
<td>55–60</td>
</tr>
<tr>
<td>Outlet temperature (°C)</td>
<td>43–45</td>
</tr>
<tr>
<td>Air volume (cfm)</td>
<td>175</td>
</tr>
<tr>
<td>Atomizing air pressure (psi)</td>
<td>30</td>
</tr>
<tr>
<td>Pattern air pressure (psi)</td>
<td>30</td>
</tr>
</tbody>
</table>

Final solution viscosity of the coating was 100 to 300 mPa•s with a solids content of 15%. Tablets were coated to a 20% weight gain. Omeprazole dissolution analysis with high-performance liquid chromatography (HPLC) was made to ensure compliance with the British and U.S. pharmacopoeia standards for drug release, detailed in Table 7. The L grade of AquaSolve HPMCAS was tested using the U.S. Pharmacopoeia (USP) method <711>. The M and H grades were tested using the British Pharmacopoeia (BP) monograph for gastro-resistant omeprazole tablets. Results of the dissolution testing are shown in Figures 20 and 21.

Table 7 – Omeprazole tablet release criteria

<table>
<thead>
<tr>
<th>BP Method</th>
<th>USP Method</th>
</tr>
</thead>
<tbody>
<tr>
<td>pH 4.5</td>
<td>pH 6.8</td>
</tr>
<tr>
<td>pH 4.5</td>
<td>pH 6.8</td>
</tr>
<tr>
<td>&lt; 10%</td>
<td>&gt; 60%</td>
</tr>
<tr>
<td>45 min</td>
<td>45 min</td>
</tr>
<tr>
<td>2 hr</td>
<td>30 min</td>
</tr>
</tbody>
</table>

Figure 20 – Dissolution testing results for AquaSolve L

Figure 21 – Dissolution testing results for AquaSolve M and H

HPMCAS under the U.S. Pharmacopoeia testing methods

HPMCAS under the British Pharmacopoeia testing methods
**Incompatibilities**
AquaSolve HPMCAS is incompatible with strong acids or bases, oxidizing agents and sustained levels of elevated humidity.

**Stability and Storage Conditions**
AquaSolve HPMCAS should be stored in a well-closed container, in a cool, dry place. In such storage conditions, HPMCAS is a stable material. HPMCAS is hygroscopic and can hydrolyze to acetic acid and succinic acid over prolonged periods of time. Hydrolysis is the main degradation pathway that is responsible for increasing amounts of free acids in storage, especially upon exposure to moisture.

**Packaging and Shipping**
The moisture content of AquaSolve HPMCAS does not exceed 5% by weight when the products are packed. Because of varying storage and shipping conditions, there is a possibility of some moisture pickup from the as-packed value. Although packaging has been designed to reduce moisture pick up, product should be stored under clean, dry conditions and used in rotation. The standard product packaging is 20 kg net weight sealed polyethylene bags, shipped in fiber drums. The type, lot number and drum number are stenciled on the outside of each drum. Read and understand the Safety Data Sheet (SDS) before using this product.

**Regulatory Status**
All AquaSolve HPMCAS grades conform to the monograph requirements of the current editions of the National Formulary and Japanese Pharmacopoeia. Please contact your Ashland representative for access to the Excipient Information Package (EIP) for further details.

**Toxicology**
AquaSolve hypromellose acetate succinate (HPMCAS) is insoluble in water and this, combined with a molecular weight range between 10,000 and 500,000 daltons, indicates that it is not orally bioavailable. There were no adverse effects in several toxicological studies, including chronic or reproductive and developmental animal studies. 1-9 HPMCAS is an approved pharmaceutical excipient for oral dosage forms. The present Inactive Ingredient Database limit for HPMCAS is 560 mg per day.

**References**
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