Ashland — from matrix to film coating, your full-service pharmaceutical technology resource

ASHLAND®

With good chemistry great things happen.™

Protect. Deliver. Stabilize. Enhance.

- Klucel™ hydroxypropylcellulose (HPC)
- Plasdone™ povidone and copovidone
- Polyplasdone™ crospovidone
- Aquarius™ film coating systems
- AquaSolve™ (AquaSolve AS™ in the United Kingdom) hypromellose acetate succinate (HPMCAS)
- Benecel™ methylcellulose and hypromellose (HPMC)
- Natrosol™ hydroxyethylcellulose (HEC)
- Aqualon™ ethylcellulose (EC)
- Aqualon™ and Blanose™ sodium carboxymethylcellulose (CMC)
- Pharmasolve™ N-methyl-2-pyrrolidone
- Cavamax*, Cavitron™ and Cavasol* cyclodextrins

Delivering pharmaceutical and nutraceutical performance

* Registered trademark owned by Wacker Chemie AG. Ashland Inc. acts as a worldwide distributor for Wacker.

Ashland Specialty Ingredients offers an unparalleled range of products to meet the needs of the pharmaceutical and nutraceutical industries. Our products offer a variety of functions as described in this brochure.

Because Ashland's products are based in both cellulosic and vinyl pyrrolidone polymer manufacturing, we provide innovative solutions through a broad range of chemistries to meet our customers' formulation needs. Our global manufacturing plants are held to strict cGMP standards, meaning our customers can depend on high-quality products, regardless of manufacturing site.

Ashland is your full-service pharmaceutical technology resource for tablet binding, film coating and disintegration; as well as excipients for controlled release and drug solubilization.

Tablet Binding

Tablet binders can make or break a formulation. To choose the right binder, a formulator must know if the desired release profile is immediate or modified. Release profiles for a given active pharmaceutical ingredient (API) can be controlled through selection of binder chemistry and molecular weight. With the exceptional range of binders produced by Ashland, you can be sure of finding the right one for your formulation. Ashland produces binders for wet granulation, dry granulation, direct compression and roller compaction, as well as hot-melt extrusion.

Klucel hydroxypropylcellulose (HPC) is our most versatile binder (different grades can be used in wet granulation, dry granulation, roller compaction or hot-melt extrusion) and is the first choice for many formulators. With the variety of functional polymers available in the Ashland portfolio, there is a high likelihood that one of our products will deliver the performance you need. We offer tablet binders for dry and wet granulation, direct compression, roller compaction, and hot-melt extrusion. See the chart for a description of which products are particularly suited for which applications.

Method	Klucel HPC	Aqualon EC	Plasdone K and C povidone	Plasdone S-630 copovidone	Benecel HPMC
Wet Granulation	×		×		×
Dry Granulation	×			×	×
Direct Compression	×	×		×	×
Roller Compaction	×	×		×	
Hot-melt Extrusion	×	×	×	×	×

Controlled-release Formulations

Achieving a desired drug-release profile has long been based on trial and error involving blends of different molecular weights of particular polymers. Ashland offers high-quality cellulosic polymers to help take the guesswork out of the process. The need for blending to achieve a particular drug-release profile can be eliminated in some cases with custom-molecular weight Benecel HPMC grades for matrix tablets. In addition, grades of Benecel HPMC are optimized for hydrophilic matrix tablets with fine, narrow particle size distributions.

Additional choices for controlled-release formulations include the following:

- Directly compressible grades of Benecel HPMC with excellent powder flow characteristics
- High-viscosity grades of Klucel HPC for sustained release by diffusion control in matrix tablets
- High-viscosity grades of Natrosol HEC for erosion-controlled release in matrix tablets tailored for poorly soluble drugs
- Aqualon EC for manufacturing sustained-release film coatings for micro-particles, pellets and tablets
- Delayed-release (enteric) Aquarius film coating systems grade based on methacrylic acid/ethyl acrylate copolymer
- Extended-release Aquarius SRX film coating systems formulations (based on Aqualon EC), for use with any API
- Enteric coatings made from AquaSolve hypromellose acetate succinate (HPMCAS) for delayed-release applications


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Tablet Film Coating

Our line of fully formulated, easily dispersed and ready-to-use Aquarius film coating systems have a range of functions to suit almost any core. With our wide selection of film coating choices, we can provide an optimal coating for your unique formulation.

Functional coating capabilities (moisture barrier, odor and taste masking, and controlled/delayed release) are based on acrylate polymers or combinations of cellulosic and other polymers and unique ingredients to offer the desired functionality.

Aquarius film coating systems present an optimum balance of film strength and adhesion—even on challenging cores—without impacting tablet dissolution. The patented Aquarius Preferred HSP and HSC coating systems are sprayable at 20% solids, for faster throughput and reduced labor and energy costs compared with conventional, lower-solids coatings.

A smooth, defect-free appearance with crisp logo definition is available with Aquarius film coating systems, whether in clear, white, pearlescent or full-color formulations. Ashland can develop new colors or expertly provide a customer match using state-of-the-art color matching software.

Ashland's Aquarius film coatings systems can be customized with various additions to address a number of special needs, including the following:

Improved adhesion

- Low-viscosity grades of Klucel HPC
- Plasdone S-630 copovidone (on hydrophobic cores)

Improved flexibility

- Low-viscosity grades of Klucel HPC

Additional enteric coating options

- AquaSolve HPMCAS grades with varying pH tolerance characteristics

Drug Solubilization

Poorly soluble APIs pose development challenges, and common techniques for improving API solubility, such as salt formation and particle-size reduction, do not always result in sufficient bioavailability required for therapeutic efficacy. Ashland has the answers for your solubility issues. AquaSolve (AquaSolve AS in the UK) hypromellose acetate succinate (HPMCAS) is a cellulose derivative with both hydrophilic and hydrophobic functional groups, making it useful as a solubility-enhancing polymer for solid dispersions. Varying the level of acetyl and succinoyl substitutions produces polymers that can bond with either hydrophilic or hydrophobic APIs to help them solubilize.

Ashland's Plasdone K povidones and Plasdone S-630 copovidone enhance the solubility of APIs in many formulations. Both products are physiologically inert, soluble in water and most pharmaceutically acceptable solvents and commonly used in both spray-dried and melt-extruded solid dispersions. Plasdone™ K povidone improves solubility and enhances bioavailability of drug actives in liquid soft-gel formulations. Plasdone™ C povidone acts as a suspending agent, solubilizer, stabilizer and viscosity modifier in parenteral formulations and liquid dosage forms.

Ashland has a number of other products to improve the solubility of the APIs in your formulations.

- The hydrophobic interior cavity and hydrophilic exterior of Cavamax, Cavitron and Cavasol cyclodextrins (available in a range of cavity sizes based on glucose units) make them useful vehicles for poorly soluble APIs and allow formulators to choose one to match particular molrcule sizes.
- Benecel HPMC can be used in spray drying and hot-melt extrusion.
- In parenteral and topical formulations, Pharmasolve N-methyl-2-pyrrolidone improves the solubility of a wide range of water-insoluble drug actives.

Tablet Disintegration

Effective tablet disintegration is necessary for drug dissolution and release. Polyplasdone crospovidone, a synthetic, cross-linked polymer, provides rapid disintegration and dissolution of oral solid dosage forms. It is available in two particle sizes to provide formulation flexibility for small and large tablets or intragranular and extragranular applications. Polyplasdone crospovidone combines rapid swelling and wicking (porosity and capillary action) mechanisms for tablet disintegration. Because it is nonionic, crospovidone provides superior dissolution of cationic drug actives.

- With its small particle size and rapid disintegration, Polyplasdone XL-10 crospovidone is preferred for orally disintegrating tablet (ODT) formulations, producing a smooth mouthfeel.
- The high compactability of Polyplasdone crospovidone makes it a good choice as a tablet disintegrant with poorly compactable drugs.
- Polyplasdone crospovidone provides disintegration at low use levels; thus, it is excellent for high-dose formulations.
- Because of its high surface area and unique chemistry, Polyplasdone XL-10 crospovidone enhances the dissolution of poorly soluble drugs vs. other disintegrants.
- At high use levels Polyplasdone crospovidone does not gel, unlike other disintegrants, so it will not retard drug release.

Technical Capabilities

Ashland offers a formidable variety of technical capabilities to meet the needs of the pharmaceutical and nutraceutical industries. Through our global network of technical service laboratories we offer assistance with formulation development, problem solving and analytical support. Our facilities are located in Wilmington, Del., USA; Hyderabad, India; Istanbul, Turkey; São Paulo, Brazil; Shanghai, China; Mexico City, Mexico and Buenos Aires, Argentina.

Our experts around the world can provide access to formulation and process development in solid dispersion technology (hot-melt extrusion and spray drying); granulation technologies (fluid bed, high shear, hot-melt extrusion) and controlled-release technologies (release-profile prediction and simulation, melt extrusion, particle and pellet coating, drug layering, matrix tablets). Additional capabilities include compaction simulation, tablet production and coating and stability studies, Ashland also has considerable expertise in characterization of powder properties (flow, particle size, surface area, morphology).

Our scientists possess extensive analytical and testing capabilities, including the following:

Analytical capabilities

- Advanced powder flow and segregation testing
- Dissolution USP I, II and III
- Differential scanning calorimetry and thermogravimetric analysis
- Melt rheology
- Microscopy—scanning electron, polarized light and high resolution digital
- Kinetic dissolution
- Advanced mechanical testing
- Size exclusion chromatography
- Karl Fischer titration
- Coulometry
- Nuclear magnetic resonance
- High-performance liquid chromatography and gas chromatography
- Infrared and ultraviolet spectroscopy
- X-ray powder diffraction
- Laser diffraction

Pilot manufacturing/testing capabilities

- Fluid beds with capacity up to 300 liters
- Several sizes of tablet coaters
- Numerous tablet presses and a MEDELPHARM Stylcam compaction simulator
- Extrusion/spheronization
- Hot-melt extrusion
- Spray-dried dispersions
- Formulation design
- Oral solid dosages
- cGMP manufacturing for clinical trials

Our staff is very involved in regulatory advocacy activities and trade associations. Among other areas of participation, Ashland was a founding member of the International Pharmaceutical Excipients Council (IPEC) Americas and participates on all committees, including the IPEC Americas Executive Committee, Compendial Review, Excipient Qualification, Regulatory Affairs and Excipient Composition. We are also active participants in IPEC Europe and founding members of IPEC China. In addition, we are active in the ASTM International D01.36 Cellulose subcommittee.

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Product Grades Available

The regulatory compliance information for all Ashland products varies by product family and grade. For specific data about the grade you are interested in please refer to our Excipient Information Packages or the Certificate of Analysis (COA), which are available from your Ashland sales representative.

Klucel™ hydroxypropylcellulose (HPC)

Grade (X = Fine)	Weight Average Molecular Weight	Typical Brookfield Viscosity (mPa•s)	Solution Concentration (%)
HF Pharm, HXF Pharm	1,150,000	1,500–3,000	1
MF Pharm, MXF Pharm	850,000	4,000–6,500	2
GF Pharm, GXF Pharm	370,000	150–400	2
JF Pharm, JXF Pharm	140,000	150–400	5
LF Pharm, LXF Pharm	95,000	75–150	5
EF Pharm, EXF Pharm	80,000	300–600	10
ELF Pharm	40,000	150–225	10

Plasdone™ povidone

Grade[a]	Weight Average Molecular Weight[b]	K-Value Viscosity
K-12	4,000	10.2–13.8
K-17	10,000	16.0–17.5
K-25	34,000	24–26
K-29/32	58,000	29–32
K-90	1,300,000	85–90
C-12	4,000	10.2–13.8
C-17	10,000	16.0–17.5
C-30	58,000	29.0–32.0

[a] C grades are pyrogen-free [b] Absolute molecular weight (SEC/MALLS)

AquaSolve™ (AquaSolve AS™ in the United Kingdom) hypromellose acetate succinate (HPMCAS)

Grade[a]	Weight Average Molecular Weight	Nominal Viscosity (mPa•s)[b]
L	114,700	2.4–3.6
M	103,200	2.4–3.6
H	75,100	2.4–3.6

[a] Available in fine and coarse particle sizes [b] NF/EP/JP viscosity method

Plasdone™ copovidone

Grade	Weight Average Molecular Weight[a]	K-Value Viscosity
S-630	47,000	25.0–31.0

[a] Absolute molecular weight (SEC/MALLS)

Polyplasdone™ crospovidone

Grade	Typical Average Particle Size (Microns)	Peroxide Specification (ppm)
Ultra[1]	110–140	30 Max
XL[1]	110–140	400 Max
Ultra-10[2]	25–40	50 Max
XL-10[2]	25–40	400 Max

[1] Ph. Eur. crospovidone monograph type A

[2] Ph. Eur. crospovidone monograph type B

Benecel™ hypromellose (HPMC)

Substitution Type	Grade	Weight Average Molecular Weight	Solution Concentration	Nominal Viscosity (mPa•s)[a]
Hypromellose 2910 "E" types	E3 Pharm	20,000	2%	2.4–3.6
	E5 Pharm	34,500	2%	4.0–6.0
	E6 Pharm	40,000	2%	4.8–7.2
	E15 PH PRM	52,000	2%	12–18
	E50 PH PRM	91,300	2%	40–60
	E4M Pharm[1]	400,000	2%	2,700–5,040
	E10M Pharm[1]	746,000	2%	7,500–14,000
Hypromellose 2208 "K" types	K100 LV PH PRM[2]	164,000	2%	80–120
	K250 PH PRM[2]	200,000	2%	200–300
	K750 PH PRM[2]	250,000	2%	562–1050
	K1500 PH PRM[2]	300,000	2%	1,125–2,100
	K4M Pharm[1]	400,000	2%	2,700–5,040
	K4M PH DC	400,000	2%	2,700–5,040
	K15M Pharm[1]	575,000	2%	13,500–25,200
	K15M PH DC	575,000	2%	13,500–25,200
	K35M Pharm[1]	675,000	2%	26,250–49,000
	K100M Pharm[1]	1,000,000	2%	75,000–140,000
	K100 PH DC	1,000,000	2%	75,000–140,000
	K200M Pharm[1]	1,200,000	2%	150,000–280,000

[a] NF/EP/JP viscosity method [1] CR grades available [2] Only CR grades available

Benecel™ methylcellulose (MC), hypromellose (HPMC) and methylhydroxyethylcellulose (MHEC)

Substitution Type	Grade	Nominal Viscosity (mPa•s)[a]
Methylcellulose	A15 LV PH PRM	12–18
	A15C Pharm	1,312–2,450
	A4M Pharm	2,700–5,040
Hypromellose 2906 "F" Types	F4 Pharm	3–5
Methylhydroxyethylcellulose	ME 50 PH PRM[2]	38–70
	ME 350 PH PRM[2]	262–490
	ME 233 P Pharm	3,100–5,700

[a] NF/EP/JP viscosity method [1] CR grades available [2] Only CR grades available

Aquarius™ film coating systems

Grade	Descriptor	Detail	Class
Preferred	HSC	High-solids coatings based on cellulosic polymers	Aesthetic
Preferred	HSP	High-solids coatings based on copovidone with cellulosic polymers for significant improvements in adhesion and sprayable solids	
Prime	-	Coatings based on traditional cellulosic polymers	
Preferred	MG	Moisture guard	Functional
Preferred	TG	Taste guard	
Preferred	OG	Odor guard	
Control	ENA	Delayed-release (enteric) coatings based on methacrylic acid-ethyl acrylate copolymer	
Control	SRX	Sustained release coatings based on ethylcellulose	

Aqualon™ sodium carboxymethylcellulose (CMC)

Weight Average Molecular Weight	Viscosity (mPa•s)	Solution Concentration	Degree of Substitution		
			0.7	0.9	1.2
725,000	1,500–3,000	1%	7HF PH		
725,000	1,000–2,800	1%	7H3SF PH		
395,000	1,500–3,100	2%		9M31F PH	
395,000	800–3,100	2%			12M31P
250,000	400–800	2%	7MF PH		
250,000	400–800	2%	7M8SF PH		
250,000	300–800	2%		9M8F PH	
90,500	25–50	2%	7LF PH		
49,000	50–200	4%	7L2P		

Blanose™ CMC

Weight Average Molecular Weight	Viscosity (mPa•s)	Solution Concentration	Degree of Substitution		
			0.7	0.9	1.2
725,000	2,500–4,500	1%	7H4XF PH	9H4XF PH	
725,000	1,500–2,500	1%	7HF PH		
725,000	1,000–2,800	1%	7H3SF PH		
725,000	1,000–2,800	1%	7HOF PH		
395,000	1,500–3,100	2%	7M31F PH	9M31F PH	12M31P
395,000	200–800	2%	7M8SF PH		12M8P
250,000	400–600	2%	7MF PH		
250,000	50–100	2%	7M1F PH		
90,500	25–50	2%	7LF PH		

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Aqualon™ ethylcellulose (EC)

Grade	Ethoxyl Substitution (%)	Weight Average Molecular Weight	Typical Brookfield Viscosity (mPa•s)[1]	Solution Concentration (%)
T10 Pharm	49.6–51.0	75,000	8–11	5
N7 Pharm	48.0–49.5	65,000	6–8	5
N10 Pharm	48.0–49.5	75,000	8–11	5
N14 Pharm	48.0–49.5	120,000	12–16	5
N22 Pharm	48.0–49.5	140,000	18–24	5
N50 Pharm	48.0–49.5	160,000	40–52	5
N100 Pharm	48.0–49.5	215,000	80–105	5

[1] Viscosity measured in 80:20 mixture of toluene/ethanol

Natrosol™ hydroxyethylcellulose (HEC)

Grade (X = Fine, W = Superfine)	Weight Average Molecular Weight	Typical Brookfield Viscosity (mPa•s)	Solution Concentration
HHX Pharm, HHW Pharm	1,300,000	3,500–5,500	1%
HX Pharm, H Pharm	1,000,000	1,500–2,500	1%
M Pharm	720,000	4,500–6,500	2%
G Pharm	300,000	250–400	2%
L Pharm	90,000	75–150	5%

Hydroxypropyl-β- and hydroxypropyl-γ-cyclodextrins

Product and Grade	Weight Average Molecular Weight	Typical Degree of Substitution
Cavasol* W7 HP Pharma	1,410	4.1–5.1
Cavitron™ W7 HP5 Pharma	1,410	4.1–5.1
Cavitron W7 HP7 Pharma	1,520	6.0–8.0
Cavasol* W8 HP Pharma	1,574	3.5-4.9

* Registered trademark owned by Wacker Chemie AG. Ashland Inc. acts as a worldwide distributor for Wacker.

Native cyclodextrin

Product and Grade	Weight Average Molecular Weight	Cyclodextrin Type
Cavamax* W6 Pharma	973	α-cyclodextrin
Cavamax* W7 Pharma	1,135	β-cyclodextrin
Cavamax* W8 Pharma	1,297	γ-cyclodextrin

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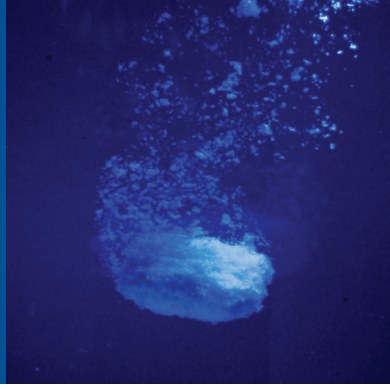
Pharmasolve™ N-methyl-2-pyrrolidone (NMP)

Pharmasolve NMP is a liquid used for crystal inhibition and solubility enhancement in parenteral applications and in veterinary medicine. Its viscosity is 1.7 cP.

Pharmaceutical Excipient Application Chart



	Product											
	Klucel™ hydroxypropylcellulose	Plasdone™ S-630 copovidone	Plasdone povidone	Benecel™ methylcellulose and hypromellose	AquaSolve™ (AquaSolve AS™ in the United Kingdom) hypromellose acetate succinate	Aquarius™ film coating systems	Polyplasdone™ crospovidone	Natrosol™ hydroxyethylcellulose	Aqualon™ ethylcellulose	Aqualon and Blanose™ sodium carboxymethylcellulose	Pharmasolve™ N-methyl-2-pyrrolidone	Cavamax*, Cavitron™ and Cavasol* cyclodextrins
Tablet Binding	✓	✓	✓	✓					✓			
Controlled-release Formulations	✓			✓		✓		✓	✓	✓		✓
Tablet Film Coating	✓	✓		✓	✓	✓			✓	✓		
Drug Solubilization		✓	✓	✓	✓		✓				✓	✓
Tablet Disintegration							✓					

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Nutraceutical Solutions

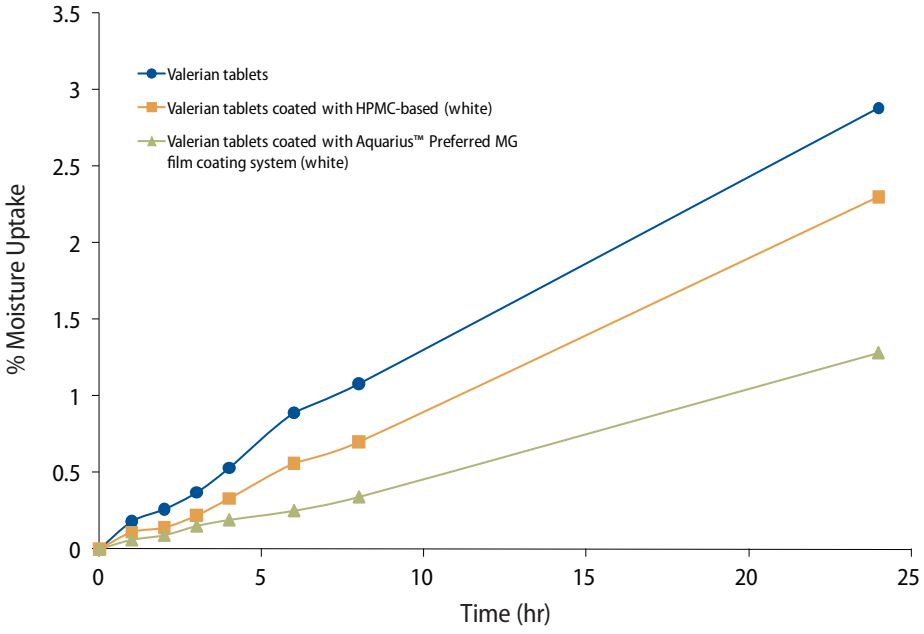
Klucel Nutra™ modified cellulose is a nonionic water-soluble polymer with a versatile combination of properties for the nutritional supplement industry. It is thermoplastic and can be molded or extruded. It provides superior tablet performance with the addition of as little as 1%. Efficient binding produces smaller tablets, requiring fewer excipients and related inventory and quality control issues and expenses. More importantly, smaller tablets lead to greater batch throughput.

Manufacturers of nutraceutical oral-dosage forms also have more coating choices with Ashland's Aquarius™ film coating systems natural colors palette. These colors were developed to meet consumer desire in the nutraceutical industry for more color-stable hues without artificial ingredients. The nutraceutical market is regulated by the U.S. and the European Union (EU). Color additives in the U.S. must comply with requirements of the U.S. Food and Drug Administration, Federal Regulations, Title 21, Part 73 and 74. Regulation (EC) No 1332/2008 and regulation (EC) No 94/36 set out rules on food additives and colors used in foods for the EU. The Aquarius coating systems natural colors palette enables manufacturers of nutraceuticals to select color coatings from a wide range of regulatory-compliant and consumer-preferred formulations.

Many nutraceutical compounds are hydrophilic and quite sensitive to ambient conditions. For additional stability of nutraceutical tablets, cores can be coated with Aquarius Preferred MG film coating system as a moisture barrier, the efficacy of which is shown in the figure.

Moisture Uptake of Valerian Tablets

Conditions: room temperature, 75% RH, open dish



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Binder Selection Guide

The choice of an appropriate binder is first made base on functionality (strength and dissolution at specified use levels). Ashland manufactures binders for wet granulation, dry granulation, direct compression and roller compaction, as well as hot-melt extrusion. Klucel™ hydroxypropylcellulose (HPC) is a versatile binder (different grades can be used in each tablet process) and is the first choice for many formulators. Beyond that, Ashland has the breadth of key functional chemistries to provide more than one solution for any tablet process.

Direct Compression

1. Klucel EXF HPC (1–6%)
2. Plasdone™ S-630 copovidone (1–8%)
3. Benecel™ A15 methylcellulose (MC) or E15 PH PRM hypromellose (HPMC) (1–5%)
4. Plasdone K-29/32 povidone (PVP) (1–5%)

Roller Compaction/Dry Granulation

1. Klucel EXF HPC (1–8%) or Plasdone S-630 copovidone (1–8%)
2. Benecel A15 MC or E15 PH PRM HPMC (1–5%)
3. Plasdone K-29/32 PVP (1–5%)

Wet Granulation, Solution Addition (Binder is pre-dissolved in granulation fluid.)

1. Plasdone K-29/32 PVP (1–5%) or 50:50 Plasdone K-90 and K-29/32 PVP (1–5%)
2. Klucel ELF or EF HPC (1–5%)
3. Benecel E5, E6 or E15 HPMC (1–5%)

Wet Granulation, Dry Binder Addition (Binder is added to dry powder components and then granulated with plain water.)

1. Klucel EXF HPC (1–5%)
2. Plasdone S-630 copovidone (1–5%)
3. Benecel A15 MC or E15 PH PRM HPMC (1–5%)
4. Plasdone K-29/32 PVP (1–5%)

Continuous Granulation Using Twin-Screw Extruder

1. Klucel EXF HPC (1–5%)
2. Plasdone K-29/32 PVP (1–5%)
3. Plasdone S-630 copovidone (1–5%)

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Benecel™ Hypromellose

Custom Grades

Custom Excipients for Robust and Predictable Controlled Release Matrix Tablets

Hypromellose (HPMC) is the most widely used polymer in hydrophilic matrix systems and has found wide-spread use in controlled-release dosage forms. Molecular weight (MW) plays a key role in dictating drug release, so formulators choose specific MW grades based on drug solubility and desired release profile.

There are a limited number of commercially available grades due to historical convention and the scale of commercial production. As a result, formulators often need to blend two or more grades to achieve a target release profile, which can be problematic.

First, determining the blend ratio is a lengthy, trial-and-error process. Second, predicting release profiles from viscosities is not straightforward, because the higher MW component often dominates the release. Third, using two or more grades in production contributes to batch-to-batch variability. A wider MW distribution or larger polydispersity index of a blend vs single component system (Figure 1) causes the release profile to be less consistent. Dissolution variability in blends is exacerbated by variations in gastrointestinal tract hydrodynamic conditions and fluid compositional factors, such as fat or bile salt content and ionic strength. Minimizing variability is of increasing importance driven by the Quality by Design (QbD) initiative.

To remedy these blending problems, Ashland has launched three intermediate-MW HPMC grades for controlled-release matrix tablets (Figure 2) - Benecel K250 PH PRM HPMC, Benecel K750 PH PRM HPMC and Benecel K1500 PH PRM HPMC. The intermediate-MW grades of Benecel HPMC provide reliability of results and eliminate the batch-to-batch variability that often results when two or more grades of HPMC are blended to provide a particular release profile. In addition, custom grades of Benecel HPMC are optimized for hydrophilic matrix tablets with fine, narrow particle size distributions.

Other MW grades can be commercialized depending on market requirements. Please contact your Ashland sales representative for more information.

Features and Benefits

- Increase predictability and reproducibility of drug release profiles
- Decrease research and development time needed to optimize blend ratio
- Decrease manufacturing time – no need to blend and manage multiple raw materials
- Opportunity to develop custom excipients

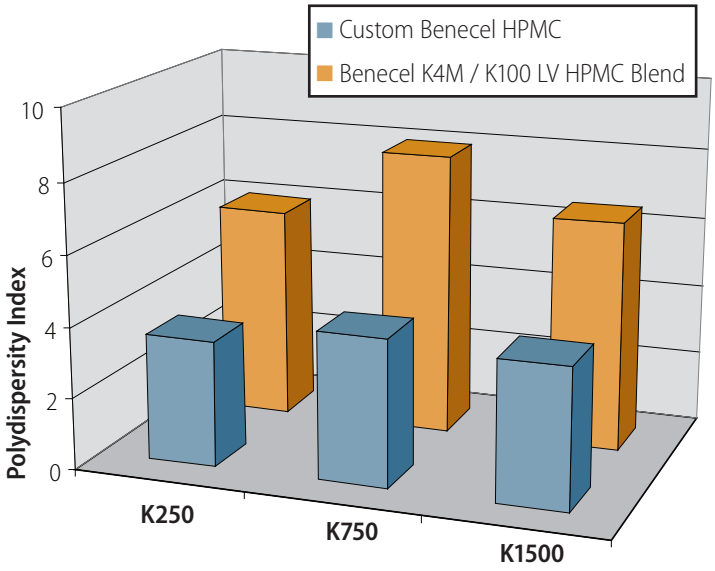

Figure 1. Comparison of polydispersity index (PDI) of Benecel K250 PH PRM HPMC, Benecel K750 PH PRM HPMC and Benecel K1500 PH PRM HPMC.

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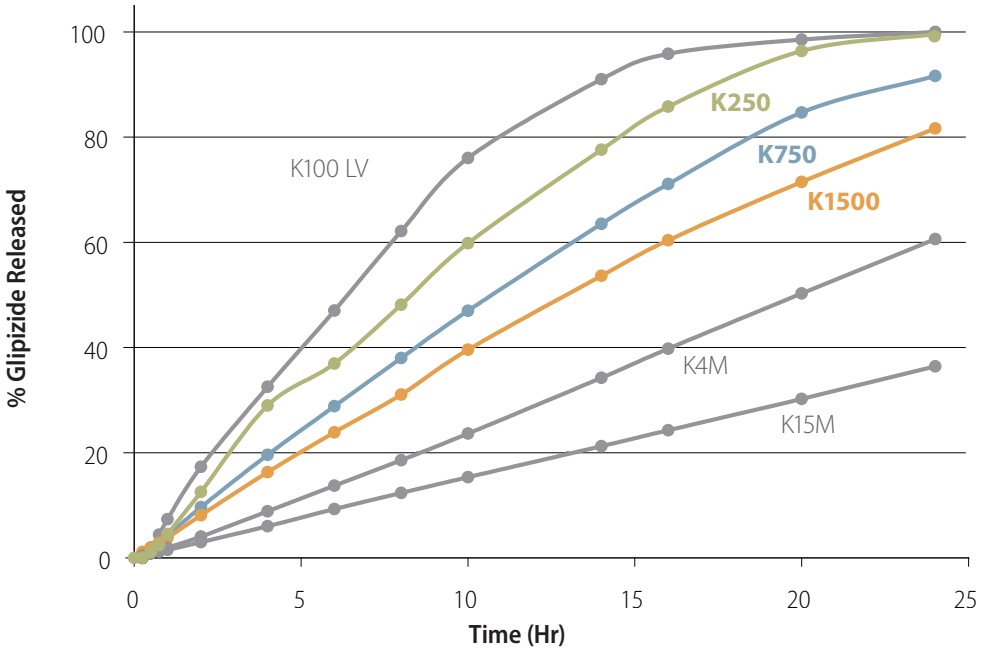


Figure 2. Release profiles for highly soluble glipizide using various grades of hypromellose. Benecel K250 PH PRM HPMC, Benecel K750 PH PRM HPMC and Benecel K1500 PH PRM HPMC fill the gap that would otherwise require a blend of commercially available grades.

Polymers for Solid Dispersions

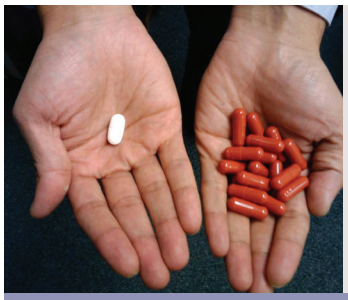
Ingredients, Process Technology Services, and Expertise for Drug Solubility Enhancement

A broad range of solutions for enhancing active pharmaceutical ingredient (API) solubility and bioavailability

Poorly soluble APIs pose development challenges, as common techniques for improving API solubility, such as salt formation and particle size reduction, do not always result in sufficient bioavailability required for therapeutic efficacy. As a result, there is increasing interest in the use of solid dispersion technology to improve the aqueous solubility and enhance the bioavailability of poorly soluble APIs. Multiple methods for preparing solid dispersions have been reported. Currently, the methods of most interest are melt extrusion and spray drying.

Ashland's Plasdone™ povidone polymers are widely used in preparing solid dispersions by melt extrusion and spray drying, as the inhibitory effect of povidone and copovidone on crystallization of drugs is well known. The thermoplastic property of Klucel™ hydroxypropylcellulose enhances processability in melt extrusion. Benecel™ hydroxypropylmethylcellulose is used in spray drying for its stability and to enhance bioavailability.

Application	Products	Benefits
Hot-melt Extrusion	Plasdone K povidone and Plasdone S-630 copovidone	Desirable thermal/rheological properties. Strong hydrogen bond acceptor. Enhances thermodynamic and kinetic stability of solid dispersions. Chemically inert. Non-pH dependent dissolution. Excellent safety profile with clinical precedence.
	Polyplasdone™ crospovidone	Extrudate is in the form of particles that can be used for direct compaction to simplify tablet preparation.
	Benecel™ HPMC	Hydrogen bond acceptor and donator. Superior stabilizer and supersaturation inhibitor. Chemically inert. Non-pH dependent dissolution. Excellent safety profile with clinical precedence.
	Klucel™ HPC	Superior thermal plasticity. Enhances processability and can be used as process aid in hot-melt extrusion.
Spray-dried Dispersions	Plasdone K povidone and Plasdone S-630 copovidone	Excellent solubility, stability and low viscosity in a wide range of solvents. Strong hydrogen bond acceptor. Enhances thermodynamic and kinetic stability of solid dispersions. Chemically inert. Non-pH dependent dissolution. Excellent safety profile with clinical precedence.
	Benecel™ HPMC	Hydrogen bond acceptor and donator. Superior stabilizer and supersaturation inhibitor. Chemically inert. Non-pH dependent dissolution. Excellent safety profile with clinical precedence.



Let us help you improve the performance of your poorly soluble APIs to do the following:

Reduce development timelines and costs

Develop delivery technologies for life-cycle management

Bring new products to market—faster

Improve safety and efficacy

Enhance patient compliance

Create new methods to rejuvenate failed/ discontinued products

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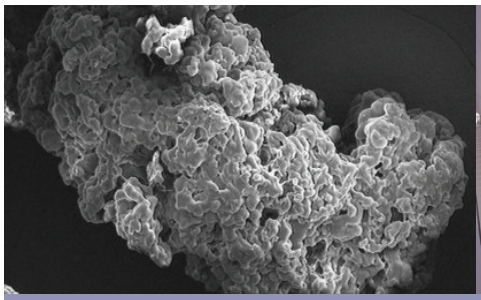
Experience with over 100 APIs

Ashland scientists have developed spray-dried dispersion formulations for over 100 APIs for over 50 pharmaceutical and biopharmaceutical clients worldwide. Our objective is to help you bring your drug products to market; therefore, Ashland pays close attention to the performance of the product, its stability, manufacturing efficiency and fit with finished dosage formulation and production. It is not unusual for pure crystalline drugs that are converted to amorphous forms to revert back to the crystalline form. However, when properly formulated, a drug-polymer solid dispersion can have a high level of amorphous stability and, in many cases, a relatively high drug load.

More ingredient solutions for poorly soluble APIs

Solution	Characteristics
Polyplasdone™ crospovidone	A unique disintegrant with high interfacial activity: improves the dissolution of poorly soluble drugs in a way that is not possible with other disintegrant technologies.
Plasdone™ C polymers	Inhibit API crystallization in injectable dosage forms.
Cavamax*, Cavasol*, and Cavitron™ cyclodextrins	Through the formation of cyclodextrin-API inclusion complexes, cyclodextrins improve the bioavailability of drugs in solid, liquid, and parenteral dosage forms.
Pharmasolve™ and 2-pyrol solubilizers	Formulation solvents increase the solubility, rate of solubilization and stability of drugs in aqueous solutions.



Solid dispersion development services from Ashland include the following:

Feasibility or proof-of-concept studies and optimization of spray-dried dispersions

Accelerated kinetic stability models to predict long-term physical stability

Kinetic solubility profiles to predict in vivo performance

Scale-up and manufacturing process development of spray-dried dispersions

Oral solid dosage formulation development and film coating

Manufacture of clinical trial materials in our cGMP facility

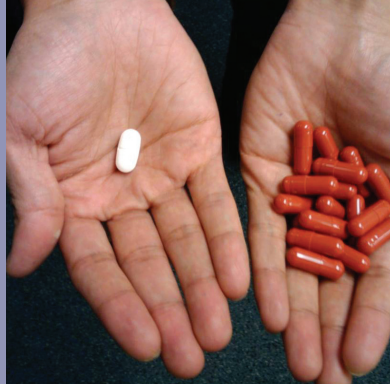
Projects can be conducted under R&D or cGMP protocols

Full cGMP documentation and analytical support

* Registered trademark owned by Wacker Chemie AG. Ashland Inc. acts as a worldwide distributor for Wacker.

AquaSolve™ Hypromellose Acetate Succinate (HPMCAS)

Versatile Pharmaceutical Polymers for Improved Solubility

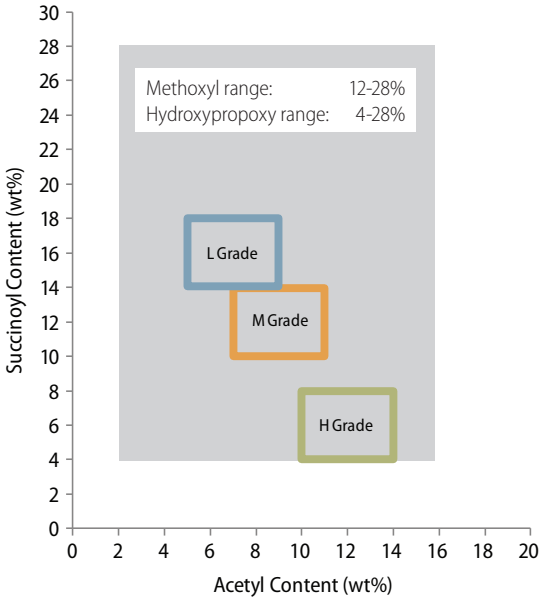


AquaSolve (AquaSolve AS™ in the United Kingdom) HPMCAS is a mixture of acetic acid and monosuccinic acid esters of hydroxypropylmethylcellulose. AquaSolve HPMCAS is used as a solid dispersion polymer for bioavailability enhancement of poorly soluble active pharmaceutical ingredients (APIs). The versatility of this polymer in addressing solubility issues is a result of its unique properties. These properties lead to enhanced absorption when HPMCAS-based solid dispersions are dosed orally.

Features and Benefits of AquaSolve HPMCAS

Feature	Benefit
Several substitution ranges	Scope for API-dependent formulation flexibility
Low solution viscosity in multiple organic solvents	Economical and controllable spray-dried dispersion processes
High T_g	Excellent physical stability due to low drug mobility
Performance matches monograph-compliant competitive products	Reduced risk in excipient sourcing and ease of interchangeability
HPMCAS is amphiphilic	Insoluble drug molecules interact with the hydrophobic regions; hydrophilic regions allow the formation of colloids in aqueous solution
Enteric polymer, so partially ionized above pH 5	Charge on the polymer minimizes the formation of large agglomerates, thus stabilizing drug-polymer colloids

AquaSolve HPMCAS is also used as an enteric coating polymer and in preparation of sustained drug-release formulations; the release rate of the API from the matrix is pH dependent.



AquaSolve HPMCAS complies with National Formulary and Japanese Pharmaceutical Excipients specifications (shaded box)

AquaSolve HPMCAS is available in three grades differentiated by degree/ratio of substitution. Each grade is available in two particle sizes. Consult the product data sheet or the excipient information package for further details on specifications. Additional substitution levels and ranges are available upon request. Detailed product information is available in the *AquaSolve™ and AquaSolve AS™ Hydroxypropylmethylcellulose Acetate Succinate Physical and Chemical Properties Handbook*.

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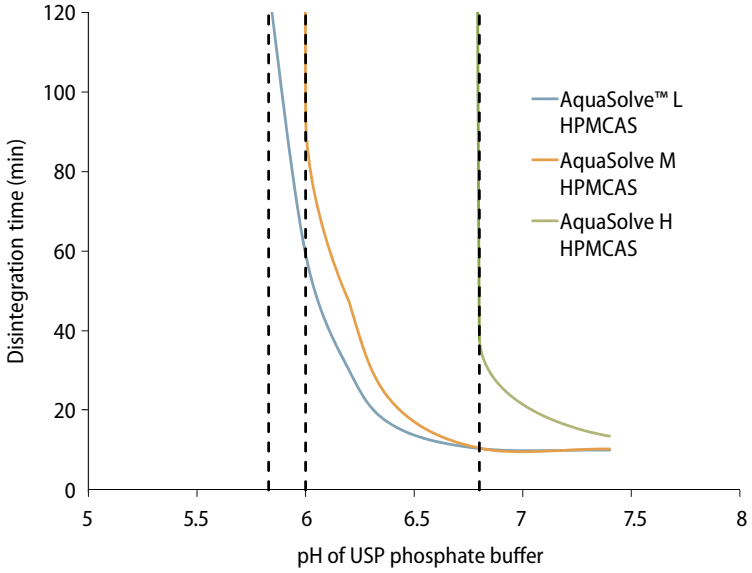
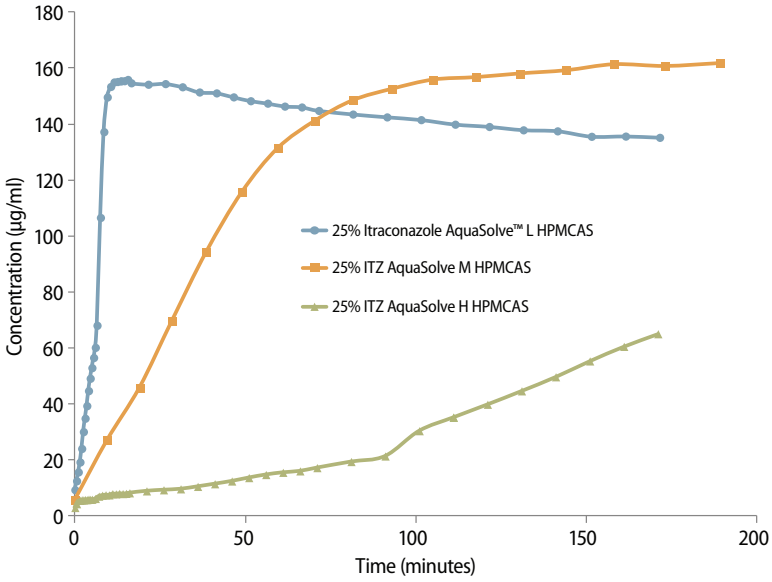
Improved Solubility Can Be Polymer Dependent

Improved solubility and bioavailabilty of an API is dependent upon which grade of polymer is selected as well as upon the API. The properties of three APIs we have worked with are shown in the table.

Property	Itraconazole	Ezetimibe	Felodipine
Tm (°C)	166.2	163	141.6
Tg (°C)	59	70	43
LogP	5.66	4.5	4.83
pKa1	3.70 (weak base)	9 (weak acid)	Neutral
Solubility (mg/l)	<1	8	19.7

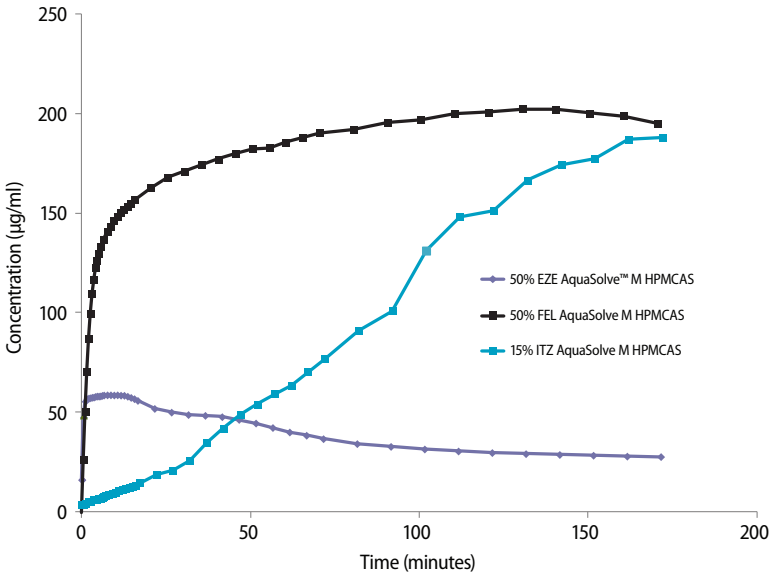


The H grade of AquaSolve HPMCAS dissolves at a higher pH than the L and M grades and so it takes longer to release in gastric fluid.



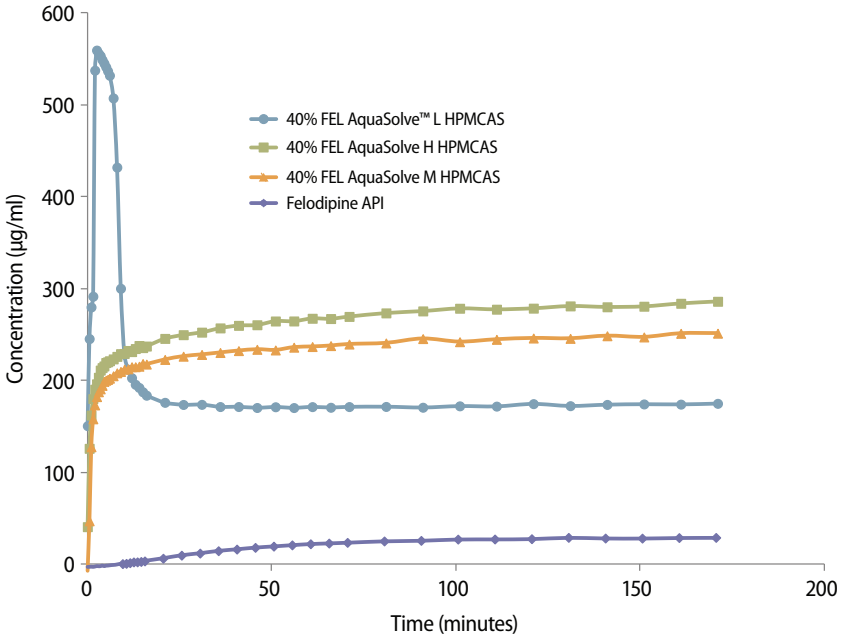
Itraconazole is a weak base and lipophilic, hence a more hydrophilic grade of HPMCAS (indicated by a higher succinoyl ratio) is required for rapid dissolution.

Improved Solubility Can Be API Dependent



Differences in solubility across APIs can be observed when using the same grade of HPMCAS with different APIs as can be seen in the variation in solubility for solid dispersions of ezetimibe, felodipine and itraconazole made with M grades of AquaSolve HPMCAS. The release profiles of the three APIs vary widely with the same (M) grade of HPMCAS.

Delayed Recrystallization



There have been a number of reports demonstrating superior performance of HPMCAS over existing polymers in terms of solubilizing efficacy in vivo and recrystallization inhibition during storage. Some HPMCAS solid dispersions exhibit characteristic spring-and-parachute shape dissolution curves, whereby a large percentage of API can be released quickly and supersaturation can be maintained for prolonged time periods. Each grade of AquaSolve HPMCAS maintains a high concentration of felodipine in solution over time, but the M and H grade curves demonstrate this prolonged supersaturation particularly well.

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Pharmasolve™ N-methyl-2-pyrrolidone

Drug Solubilizer

Product overview

A water-miscible polar aprotic solvent with high interfacial activity, Pharmasolve N-methyl-2-pyrrolidone (NMP) is used as a drug solubilizer and penetration enhancer in parenteral and topical dosage forms. Pharmasolve NMP has a history of use with many different drug actives and routes of administration. Ashland offers a high quality, cGMP grade of NMP specifically for use in veterinary products. Ashland's grades of Pharmasolve NMP conform to the monographs for n-methylpyrrolidone and n-methyl-2-pyrrolidone in Ph. Eur and JPE, respectively.

Drug solubility in parenteral applications

For poorly soluble drugs administered parenterally, the number of suitable vehicles to dissolve or disperse the formulation is limited. One option is to use Pharmasolve NMP. Enhanced solubility is seen with select drugs when Pharmasolve NMP is included in the formulation because of the polar nature of the molecule.
In a review of the literature, NMP has appeared in veterinary applications as a solubilizing agent for several antibiotic and sulfa drugs. The literature describes injectable compositions with high concentrations of florfenicol, an antibiotic with low aqueous solubility containing 10 to 65% w/w NMP (1). The compositions have good physical and chemical stability with desirable viscosity for good syringeability over a wide temperature range. In another example, oxytetracycline antibiotic compositions with 25 to 50% w/w NMP and 1 to 10% w/w povidone reduce swelling or pain typically associated with tetracycline-type compounds (2). Long-acting, injectable parasitical compositions with ivermectin and 40–65% w/v NMP and Plasdone™ K-17 povidone have also been developed (3). Sulfadimethoxine and sulfamethazine are used as therapeutic agents in long-lasting injectables for veterinary applications. NMP is present in the formulations as a cosolvent in concentrations from 40 to 65% w/v in water (4). The compositions may also include povidone.

Penetration enhancement in topical applications

Several published studies discuss the use of NMP as a strategy to enhance the permeability of drugs through the skin. In one study, the occluded vasoconstrictor assay was used to assess the effect of penetration enhancers on the topical bioavailability of a representative steroid, betamethasone 17-benzoate (5). Of all the penetration enhancers investigated in the study, the researchers concluded that only NMP significantly increased the bioavailability of betamethasone 17-benzoate. In a separate study, the addition of 2% NMP in different ointment formulations of mefenamic acid increased the penetration of the drug by 1.5 times (6). Several topical formulations have also been developed in which NMP solubilizes griseofulvin, an antibiotic used to treat fungal infections of the skin and nails in animals (7). In addition, the literature cites the use of theophylline as an active ingredient to provide useful topical anti-inflammatory activity in animals (8). This work describes novel topical compositions comprising 0.1 to 1% theophylline and 5 to 99% NMP.

Benefits

- Enhanced solubility of select drugs
- Enhanced permeability of drugs through the skin
- Increased bioavailability of select drugs
- Inherently stable material
- Resistant to hydrolysis
- Proven in antibiotics and sulfa drugs, steroids, and anti-inflammatory compounds

Physical and chemical properties

Stability

Pharmasolve NMP is a stable material. It is exceedingly resistant to hydrolysis, except at pH below 1.5 or above 11.0. Table 1 describes the typical physical and chemical properties.

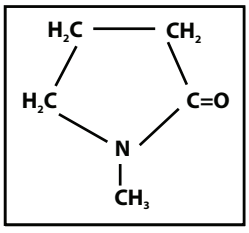

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Table 1
Typical properties

Appearance	Clear, colorless liquid
Purity	>99.7%
Viscosity (cP at 25°C)	1.7 as is
Flash Point (°C)	93 (194°F)
Vapor Pressure (mm Hg @ 20°C)	0.27
Boiling Point (°C)	202 (395.6°F)

Viscosity

The viscosity of anhydrous Pharmasolve™ NMP decreases with temperature (Figure 1). The viscosity of an aqueous mixture of water with Pharmasolve NMP increases until about 30% water and decreases with continued addition of water (Figure 2).

Figure 1
Effect of temperature on viscosity of NMP

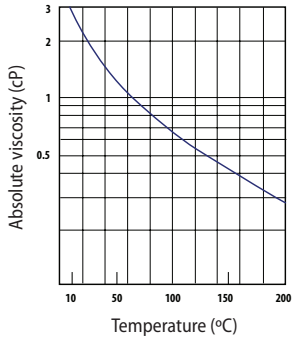
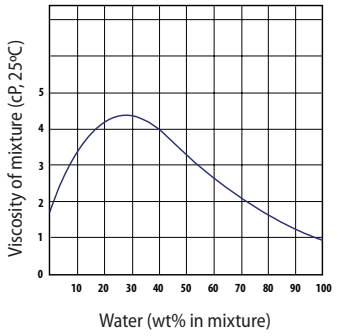


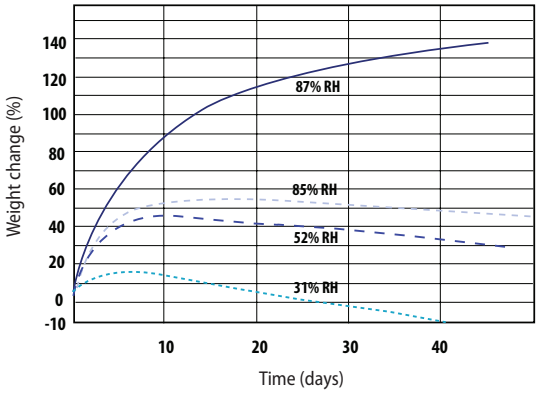
Figure 2
Viscosity of mixtures of water with NMP



Effect of humidity

At high relative humidity, above 80%, weight gain due to hydration is rapid and continues for an extended time period. At lower humidity, the absorption of water is slower and the weight change peaks after 10 days as a result of the gradual evaporation of NMP. Eventually, the rate of absorption of water gradually decreases and the loss of volatilization of NMP is more substantial (Figure 3).

Figure 3
Effect of humidity on rate of weight change of NMP



Note: Static tests conducted in desiccators over appropriate saturated salt solutions: calcium chloride (31% RH), sodium acid sulfate (52%), magnesium acetate (65% RH), sodium carbonate (87%) RH. Two dishes were employed for (1) determination of weight change and (2) periodic water

References:
1. Schering Corporation, "Pharmaceutical compositions of florfenicol," US patent 5,082,862, January 1992.
2. Bimeda Research and Development, Ltd, "Method of reducing the swelling or pain associated with antibiotics compositions," US patent 4,772,460, September 1988.
3. Biogenesis S.A., "Long acting injectable parasiticidal composition and the process for its preparation". US patent 6,054,140, April 2000.
4. Pfizer, Inc., "Long acting sulfonamide injectable compositions," Eur patent application EP19800302190, Filed June 1980.
5. Barry, B.W., D. Southwell and R. Woodford, "Optimization of bioavailability of topical steroids: Penetration enhancers under occlusion," *J. of Investigative Dermatology*, 82:49-52, 1984.
6. Naito, S., S. Nakamori, M. Awataguchi, T. Nakajima, and H. Tominaga, "Observations on and pharmacokinetic discussion of percutaneous absorption of mefenamic acid," *Int. J. Pharmaceutics*, 24: 127-147, 1985.
7. Stoughton, R.B., "Composition and method for topical administration of griseofulvin," US patent 3,932,653, January 1976.
8. Schorer, R.A., "Topical anti-inflammatory composition and method of use," US patent 3,957,994, May 1976.

Benecel™ PH DC hypromellose (HPMC)

For Direct Compression Controlled-release Applications

Direct compression is a preferred process for manufacturing tablets, because it is simple and cost effective. However, direct compression of controlled-release formulations has traditionally been a challenge due to limitations of controlled-release excipients, which are used at high levels and can result in poor compressibility and final product content uniformity.

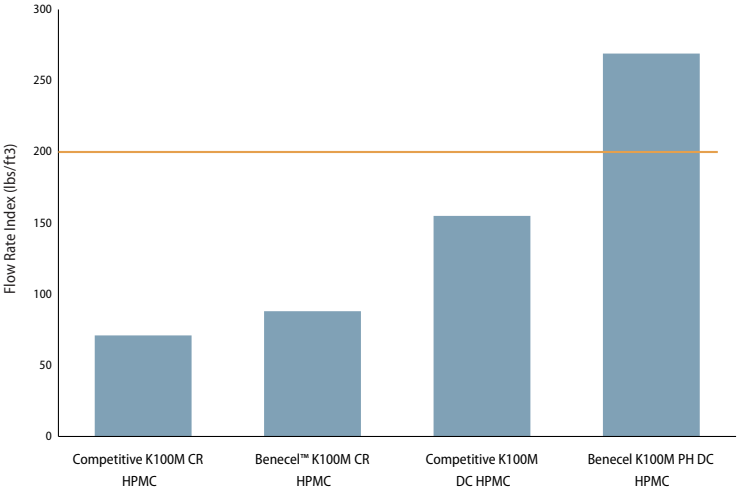
Typical controlled-release polymers have a fibrous nature, small particle size, strong inter-particle cohesion and surface charge, which lead to poor flow in pharmaceutical unit processes. Formulators often have to use a granulation step to overcome these challenges to powder flow.

Benecel™ PH DC hypromellose (HPMC) grades are designed for superior flow and compaction in direct compression controlled-release applications.

Benefits offered by these grades include the following:

- Improved powder flow
- Improved content uniformity
- Dissolution profiles comparable with controlled-release grades of HPMC
- Reduced processing time and production costs

Enhanced Flow



A two-fold improvement in the flow rate is seen in comparison with competitive K100M DC HPMC and standard K100M CR HPMC.

Enhanced flow as a result of low inter-particle cohesion and higher bulk density: Flow rate index greater than 200 lbs/ft^3 indicates good flow.

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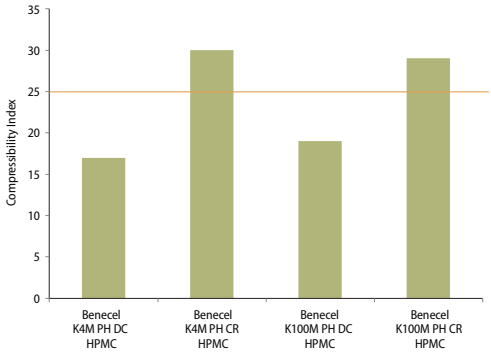
Improved Content Uniformity

The compressibility index (CI) is defined as

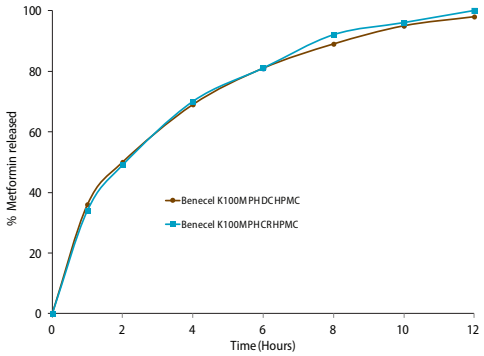
$$\frac{100 \times (Td - Bd)}{Td}$$

where Td is tap density and Bd is bulk density.

A high CI (>25) indicates a greater difference between the tap and bulk densities, leading to poor flow, which causes poor content uniformity.



Dissolution Profile Consistent with Regular CR grades



Similar release profiles as HPMC CR grades in wet-granulation applications, create the opportunity for drop-in replacement.

Cost Savings

Using these grades in direct compression applications can provide a significant cost savings over traditional wet-granulation applications because of the simplified manufacturing process.

Ideal Choice

Benecel PH DC grades of HPMC are controlled-release excipients that offer better powder flow and compaction properties than competitive products, for direct-compression applications. These grades are an ideal choice for high-quality dosage forms.