Hydroxypropyl Methyl Cellulose Acetate Succinate (HPMCAS) based Solid Dispersions

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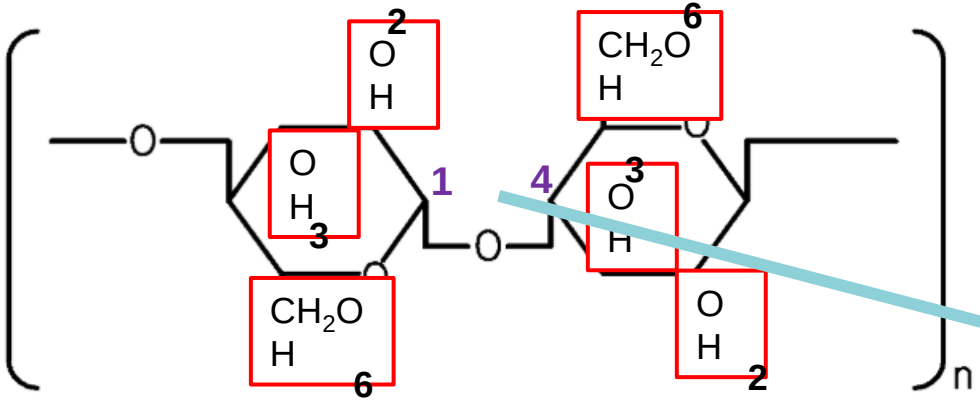
Hydroxypropyl Methylcellulose (HPMC)



Cellulose

- -OH at 2,3 and 6 is available for substitution

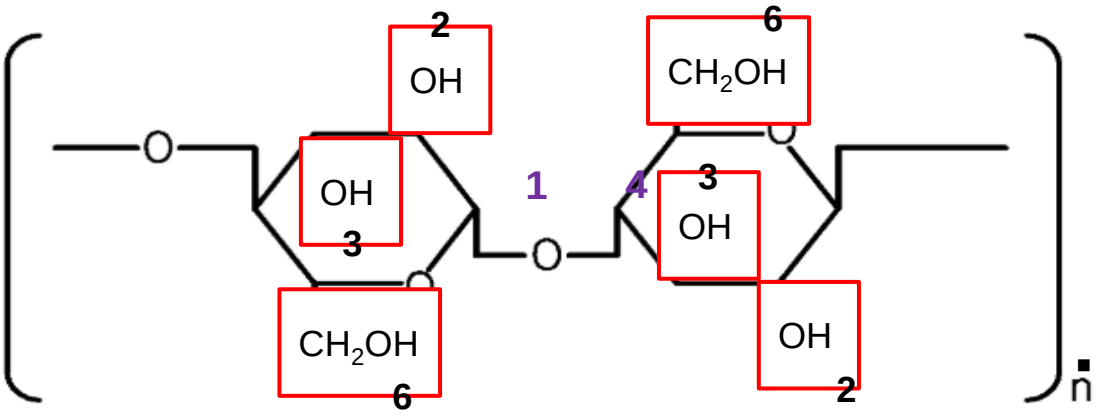
Anhydroglucose units
With 1,4 β glyosidic bond

Substitution	Chemical Composition
Me	$-CH_3$
HP	$-CH_2CH(CH_3)OH$
HPMe	$-CH_2CH(CH_3)OCH_3$
Ac	$-COCH_3$
Su	$-COCH_2CH_2COOH$
HPAc	$-CH_2CH(CH_3)OCOCH_3$
HPSu	$-CH_2CH(CH_3)OCOCH_2CH_2COOH$

HPMC

Hydroxypropyl Methylcellulose Acetate Succinate (HPMCAS)

Cellulose



HPMCAS shows pH-dependent solubility, and soluble only >pH 5.5

Substitution	Chemical Composition
Me	-CH_3
HP	-$CH_2CH(CH_3)OH$
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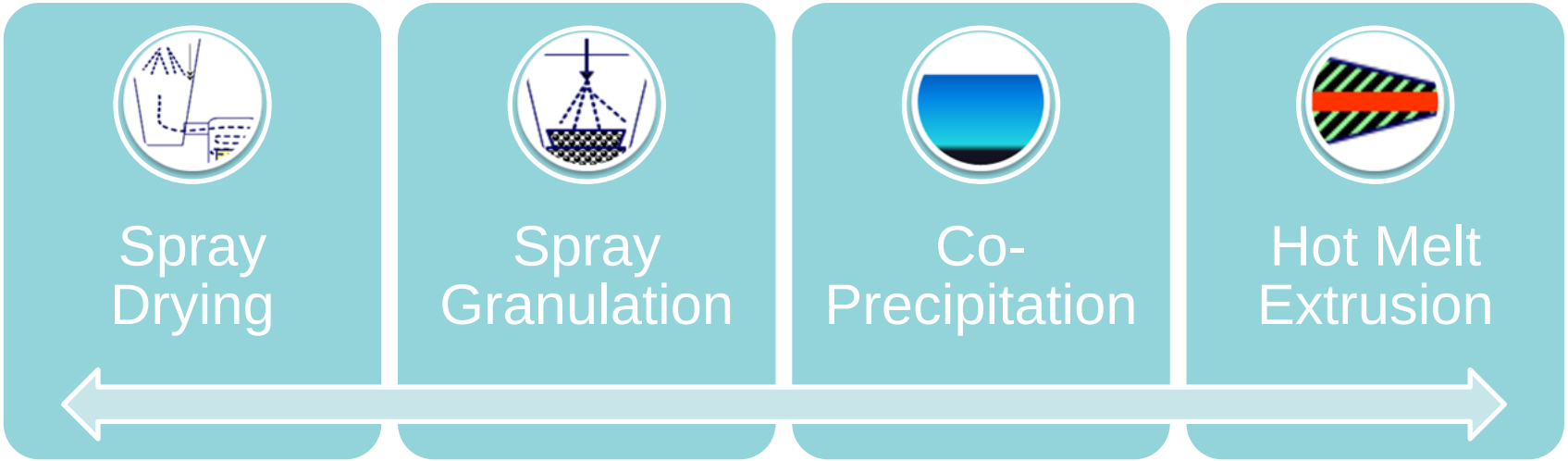
Ac	-$COCH_3$
Su	-$COCH_2CH_2COOH$
HPAc	-$CH_2CH(CH_3)OCOCH_3$
HPSu	-$CH_2CH(CH_3)OCOCH_2CH_2COOH$

HPMCAS

Acetyl; Hydrophobic

Succinoyl; Hydrophilic

Amorphous Solid Dispersion (ASD) Technologies



Mahmah, O.; Tabbakh, R.;Kelly, A; Paradkar, A., J. Pharm. Pharmacol. 2014, 66, 275–284. Sarode, A.L.; Obara, S.; Tanno, F.K.; Sandhu, H.; Iyer, R.; Shah, N., Carbohydrate Polymers 2014, 101, 146-153. Yanbin, H.; Wei-Guo, D., Acta Pharm Sin B. 2014, 4, 18-25. Shin-Etsu Technical Information A-028 (2010).

Challenge: Spray Drying - Need for Large Volume of Organic Solvent

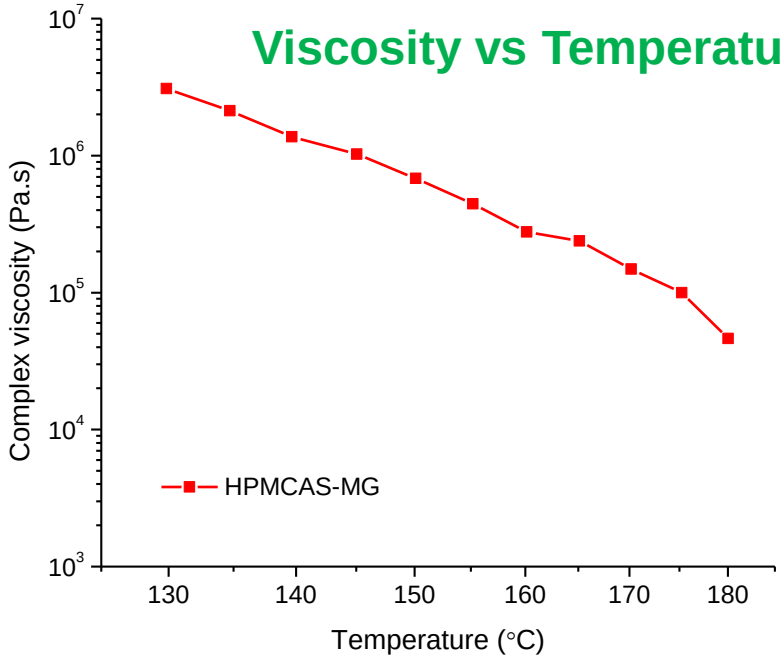
An example

Preparation of Spray-Dried Dispersions (SDDs). SDDs were made at labscale, using the following method exemplified for a dispersion of Compound 2. A solution of Compound 2 and polymer was made by dissolving 133.0 mg of [R-(R*,S*)]-5-chloro-N-[2-hydroxy-3-(methoxymethylamino)-3-oxo-1-(phenylmethyl)propyl]-1-H-indole-2-carboxamide (Compound 2, Table I) and 67.0 mg of HPMCAS-MF (Shin Etsu, containing 23.4% methoxyl, 7.2% hydroxypropyl. 9.4% acetyl, 11.0% succinoyl, MW=8.0×10^4, Mn=4.4×10^4) in 10 g of HPLC grade acetone (Burdick & Jackson). The compound/polymer solution was then placed in a 20 mL syringe that was then inserted into a syringe pump. Solvent was rapidly removed from the above solution by spraying into a small spray-drying apparatus called a "Mini" spray drier, which

- Preparation ASD for an experimental drug with HPMCAS
- 10 g of acetone was used to dissolve 133 mg of drug and 67 mg of HPMCAS
- Drug to solvent ratio, 1: 75
- For 100 kg drug, 7,500 kg (or ~10,000 L) of acetone needed

Curatolo, W., Nightingale, J.A. and Herbig, S.M., 2009. Utility of hydroxypropylmethylcellulose acetate succinate (HPMCAS) for initiation and maintenance of drug supersaturation in the GI milieu. *Pharmaceutical research*, *26*(6), pp.1419-1431.

Challenge: HME - Processability of HPMCAS



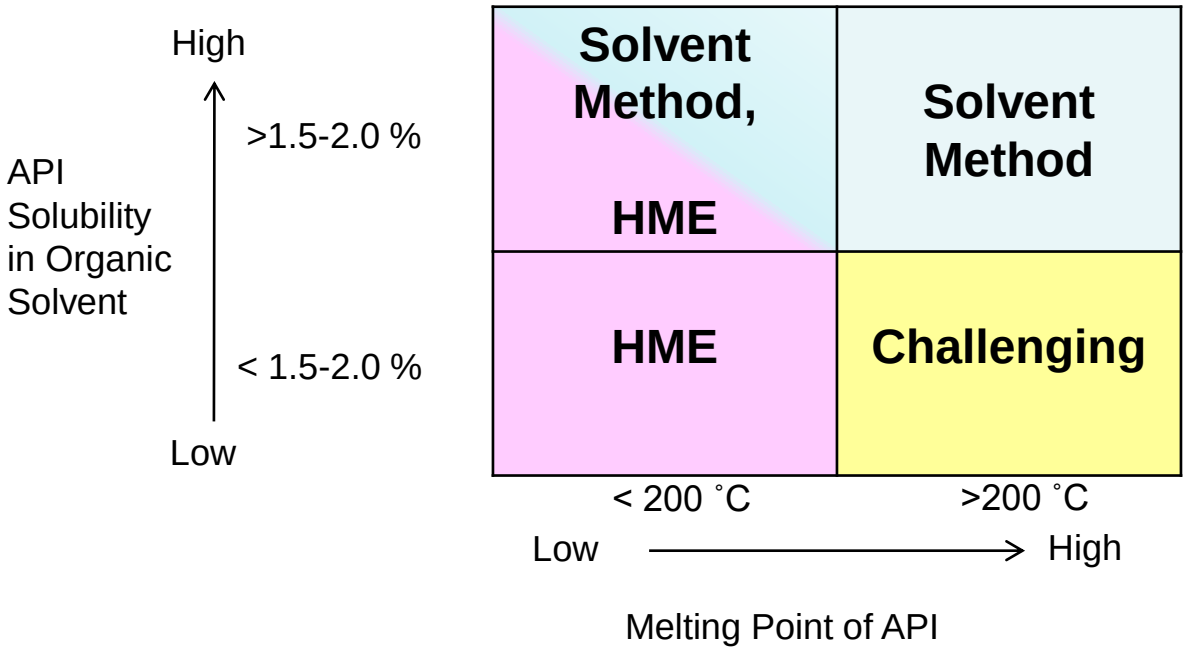
- High melt viscosity
- Extrudable only ≥170°C and potential degradation

1,000 to 10,000 Pa.s
Recommended for extrusion and dissolve drug in polymer

- Melt viscosity of HPMCAS at 0.1 rad/sec angular frequency and 0.5% oscillation strain

*Gupta SS, Parikh T, Meena AK, Mahajan N, Vitez I, Serajuddin AT. Effect of carbamazepine on viscoelastic properties and hot melt extrudability of Soluplus®. International journal of pharmaceutics. 2015 Jan 15;478(1):232-9.

Process Choice



HPMCAS Substitution

HPMCAS is a cellulose polymer with four types of substituents semi randomly substituted on the hydroxyls:

- Methoxy with a mass content of 12-28%
- Hydroxypropyl with a mass content of 4-23%
- Acetate with a mass content of 2-16%
- Succinate with a mass content of 4-28%

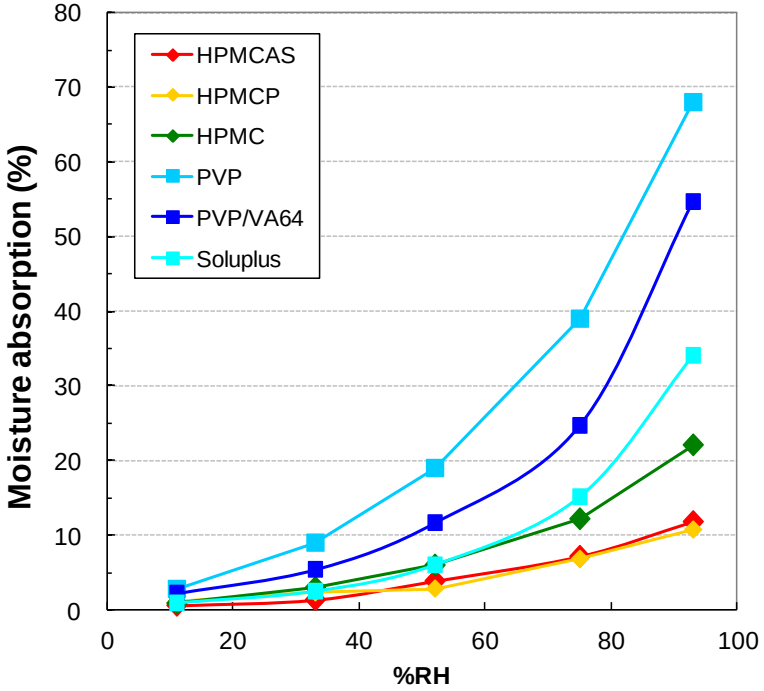
- The succinate groups has a pKa of about 5, and therefore, the polymer is less than 10% ionized at pH values below about 4 and is at least 50% ionized at pH values of about 5 or higher.
- Due to the presence of relatively hydrophobic methoxy and acetate substituents, HPMCAS is water insoluble when unionized (about pH<5) and remains predominantly colloidal at intestinal pH 6.0-7.5.
- Spray Dried Dispersions are formed using HPMCAS in its un-ionized form. In this form it is quite soluble in volatile organic solvent such as methanol and acetone and can be a good candidate for spray drying.

*Dwayne TF, Ravi S, Marshall C, Daniel, TS, JAS Nightingale, Hydroxypropyl-methylcellulose acetate succinate-based Spray-Dried Dispersions: An Overview. molecular pharmaceutics. 2008 Oct. 13:1003-19.

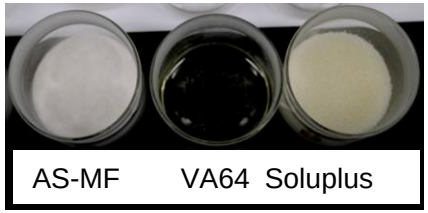
Different Grades of HPMCAS

Grade of HPMCAS	Succinoyl:Acetyl Ratio	Succinoyl content	Acetyl content	Dissolving pH
HPMCAS-L	Highest Succinoyl content	14-18%	5-9%	pH ≥ 5.5
HPMCAS-M	Meduim Succinoyl Content	10-14%	7-11%	pH ≥ 6.0
HPMCAS-H	Lowest Succinoyl Content	4-8%	10-14%	pH ≥ 6.5

Equilibrium Moisture Content



93%RH, 30days



PVP-based polymers are very hygroscopic.

・Soluplus swells at high moisture

Why HPMCAS? - Dissolution Advantage

- **Amorphous drug:** High solubility
- **HPMCAS:** Maintains **supersaturation** for a longer period of time
- **Better stability:** **HPMCAS** is relatively less hygroscopic and exhibits high glass transition temperature **(Tg)** even at high humidity

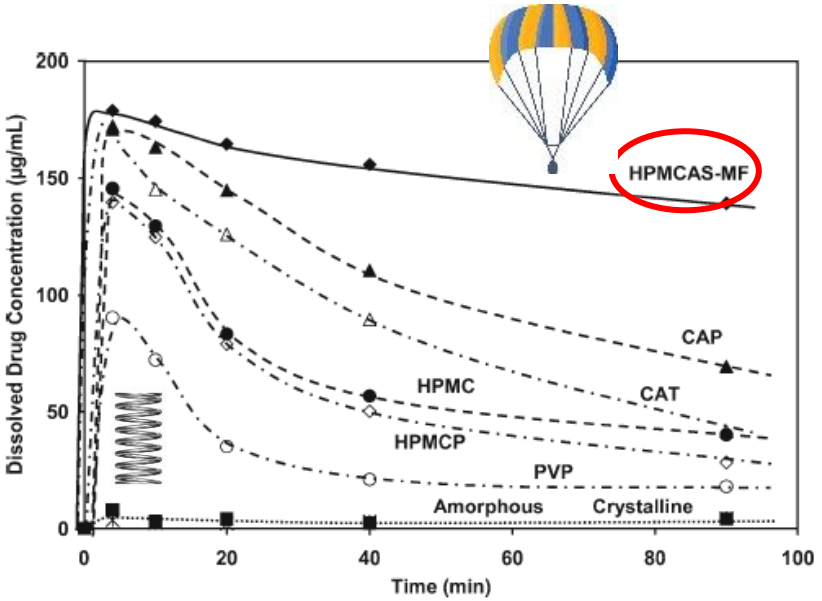


Fig. 7. Dissolution performance of SDDs made with Compound 5 and various polymers, at 10% drug loading. Dissolution was carried out using the microcentrifuge dissolution test in PBS at 37°C, with a 200 µg/ml total concentration (dissolved plus undissolved drug).

*Curatolo W, Nightingale JA, Herbig SM. Utility of hydroxypropylmethylcellulose acetate succinate (HPMCAS) for initiation and maintenance of drug supersaturation in the GI milieu. Pharmaceutical research. 2009 Jun 1;26(6):1419-31.

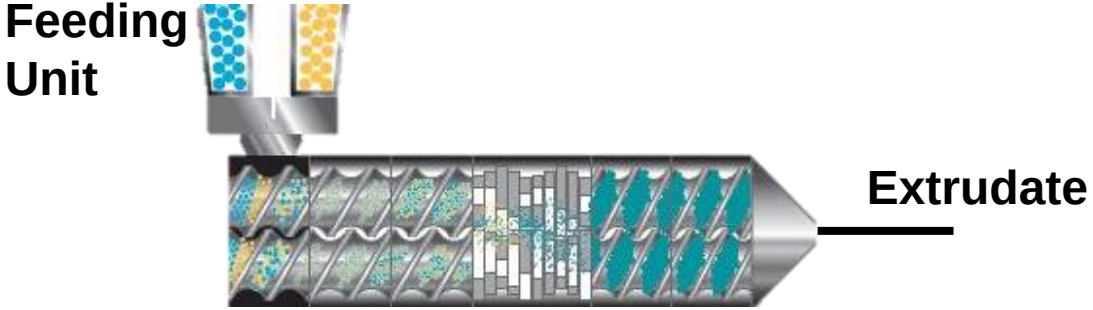
Uniqueness of HPMCAS - Dissolution Advantage

- The dissolution advantage of HPMCAS is due to two reasons:
  - Above pH 5 the polymer is at least partially ionized, and this charge supports stable nanosized drug polymer aggregates (colloidal particles) which do not merge into larger.
  - HPMCAS is amphiphilic, and hydrophobic regions on the polymer provide sites for drug association, while hydrophilic regions permit the stable formation of hydrated nanosized colloidal structures in aqueous media.
- HPMCAS is relatively less hygroscopic and exhibits high glass transition temperature (Tg) even at high humidity. The Tg of HPMCAS is around 122C and it has a Tg of approximately 95C at 50%RH. PVP has a higher Tg on 0% RH and around 50C at 50% RH.
  - In order to maintain a homogeneous solid amorphous dispersion, it is important that the molecular mobility of the dispersion (drug and polymer) be low, to minimize diffusion and crystallization of drug molecules during storage of solid dispersion formulation.

*Curatolo W, Nightingale JA, Herbig SM. Utility of Hydroxypropyl-methylcellulose acetate succinate (HPMCAS) for initiation and maintenance of drug supersaturation in the GI milieu. Pharmaceutical research. 2009 Jun 1;26(6):1419-31.

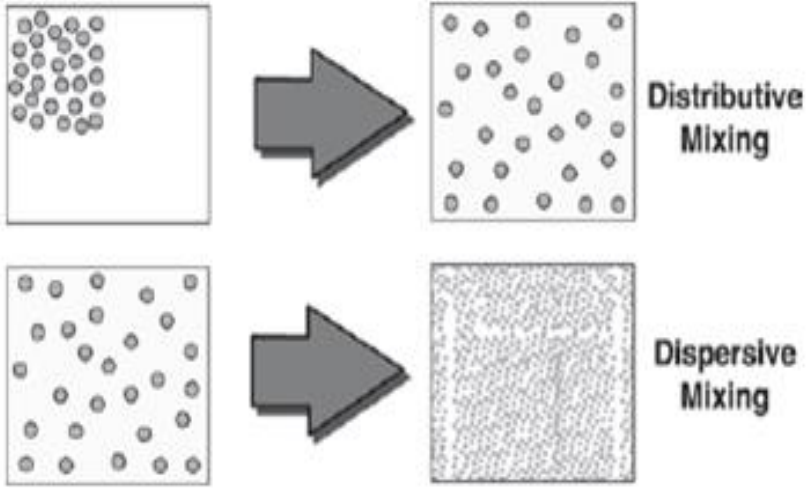
Solid Dispersion by HME

- Solvent free, continuous process
- API and polymer homogenized through extrusion



- Downstream of SD important step
- Maag Automatic provides solutions for pelletizing of extrudates

Mixing & Screw Elements



Reprint: Extrusion Handbook

Reprint: Google

Powder Morphology of AQOAT®

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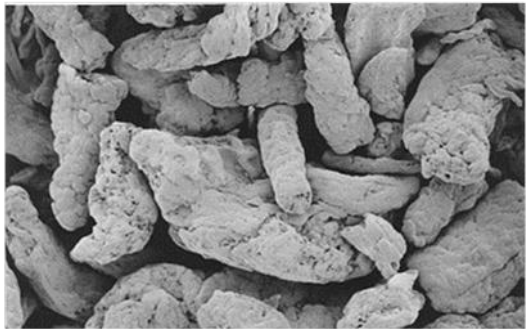
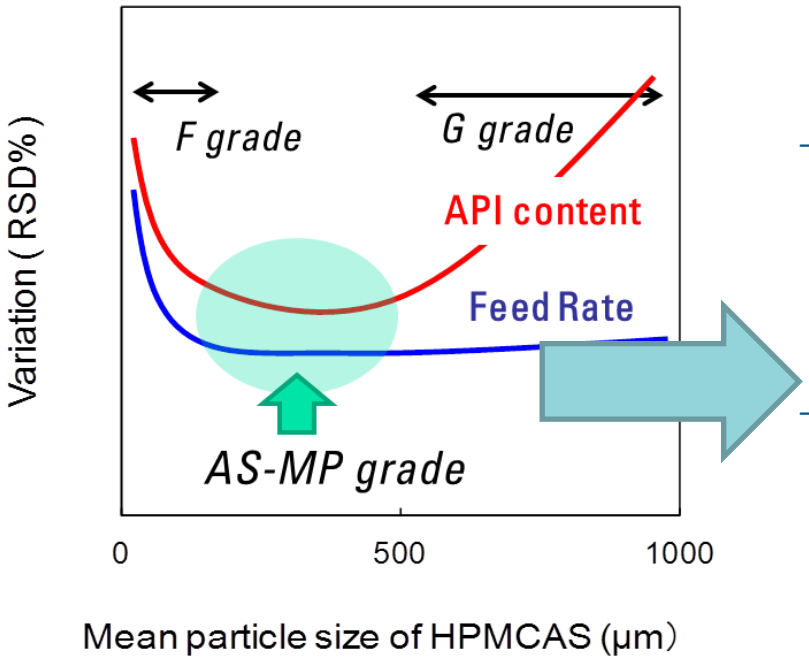
F-Grade 1000x
Approx. 5 μm

MP-Grade 50x
Approx. 70-300 μm



G-Grade 50x
Approx. 500-1000 μm

Powder properties



- Feed rate test
  Single screw powder feeder, 55 mm diameter, 10 rpm
- API content test
  AQOAT® blended with Vitamin C powder(3:1), analysis of API content after feeding
- New **MP grade** provides:
  Constant feed rate
  Excellent miscibility with API

Mixing Uniformity

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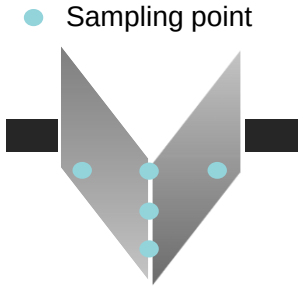
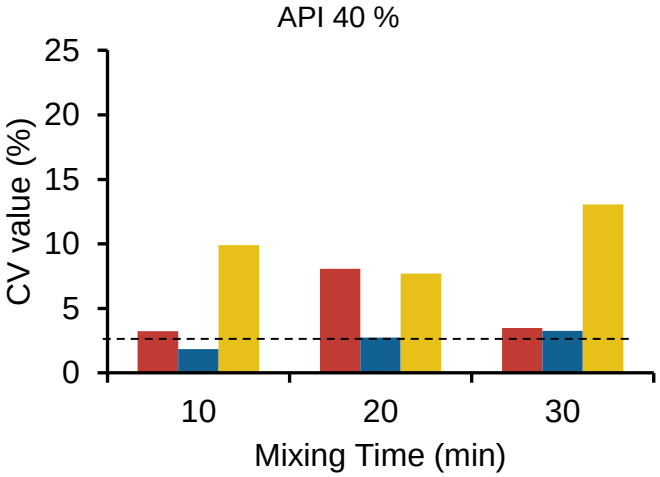
Trial with Nifedipine (app. 15μm)

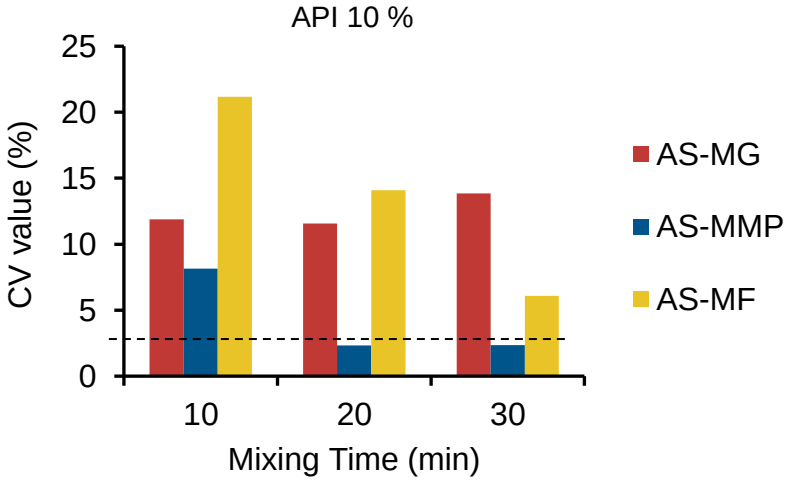
· AS-MMP can mixed uniformly compare to the AS-MG and AS-MF due to the desirable powder properties



Mixed Nifedipine (app. 15μm) and AS by V shape rotating mixer in each time

Sample was picked at 5 sampling point and API content is checked by UV spectroscopy





Differential scanning calorimetry

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<u>See the heat capacity of samples</u>

Basic study (pure sample)

- Melting temperature
- Glass transition temperature
- Crystallization temperature

Applied study (binary mixture)

- Solubility of API and Polymer
- Stability of solid dispersion

Grass transition temperature evaluated by DSC

	Grade	Tg (°C)
HPMC	Pharmacoat 606	146
	60SH-50	165
HPMCAS	AS-LG	122
	AS-MG	122
	AS-HG	122
HPMCP	HP-50	139
	HP-55	138

- Glass transition temperature (Tg) is temperature above which amorphous molecule increase mobility
- Extrusion temperature > Tg + 20 °C is recommended to extrude formulation (API might reduce Tg)

Difference in Rheometor

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MFI tester

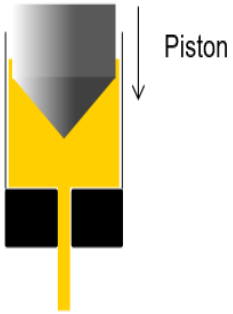
- Single point measurement.
- OK for very similar materials.
- Single temperature with single weight.

Shear rheometer

- Shear dependent behaviour.
- Temperature effects.
- Viscous and elastic behaviour.

Capillary rheometer

- Pressure flow.
- Temperature effects.
- Higher shear rates.



Tim. Gough et. Al., Polymer Rheology, Shin-Etsu Technical Seminar June 2017

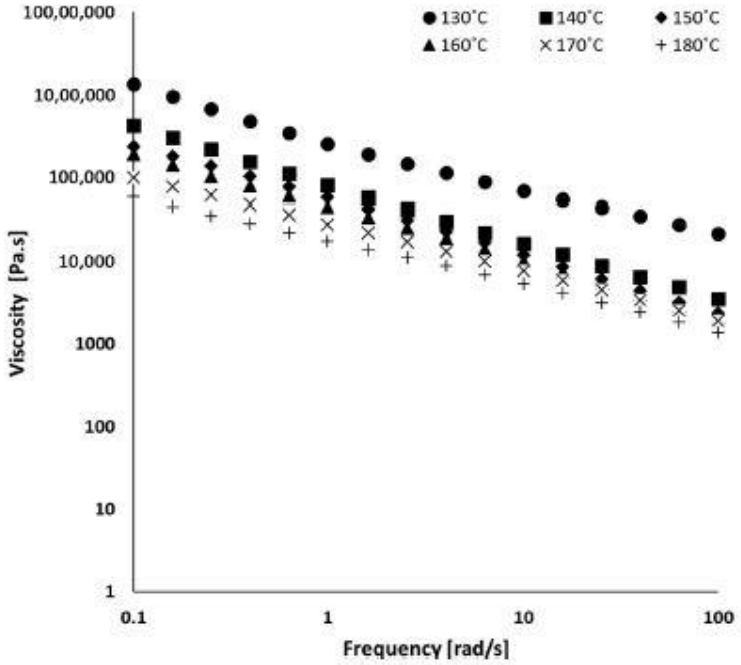
Shear Rheometer

- Confidential -

Viscometric study

- Dynamic viscosity is also can be measured by shear rheometor
- Measurement can be done at lower temperatur and shear than capillary rheometor

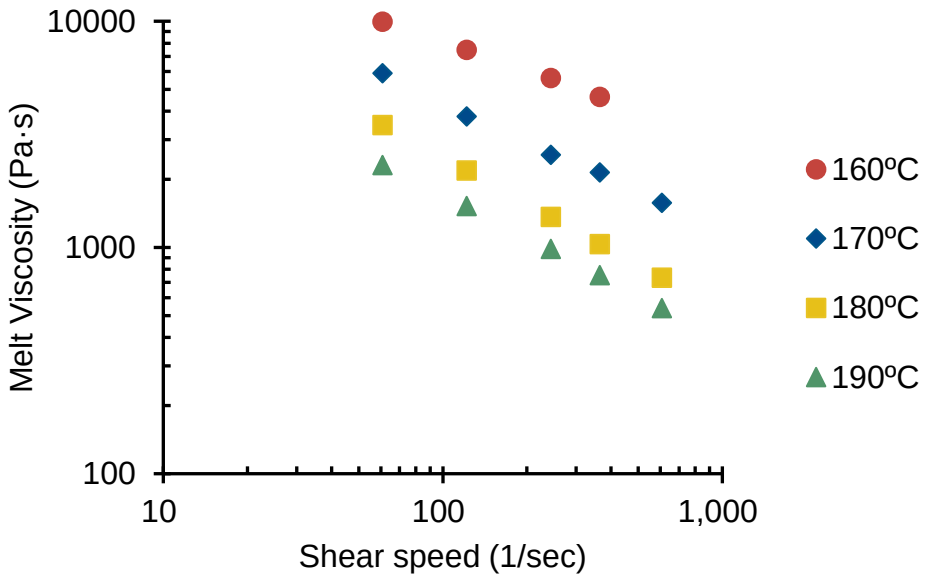
Dynamic viscosity of HPMCAS drops significantly from 130 to 140C, at a temperature it behave as a polymer melt. From 140 to 180C the sensitivity of dynamic viscosity on temperature is small.
If HPMCAS is extruded in the range of 130-140C it will require a good temperature control, otherwise small variation will affect result in variation of viscosity affecting the process/product stability.

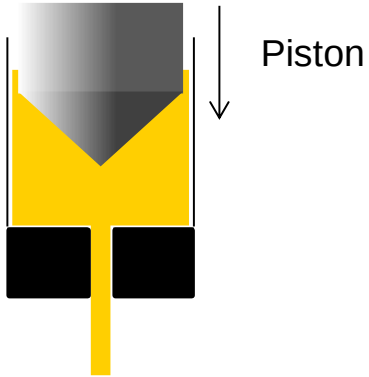


Jiannan Lu *et. al*., Advances in Polymer Technology, Vol. 37, Issue 1, 2016,

Capillary Rheometer

– Could measure the viscosity with similar method to HME (pressure driven flow)





Capillary Rheometor
Capilograph (Toyo Seiki co.)

Sample: AS-MG
Heating Time: 5min

Thermal changing

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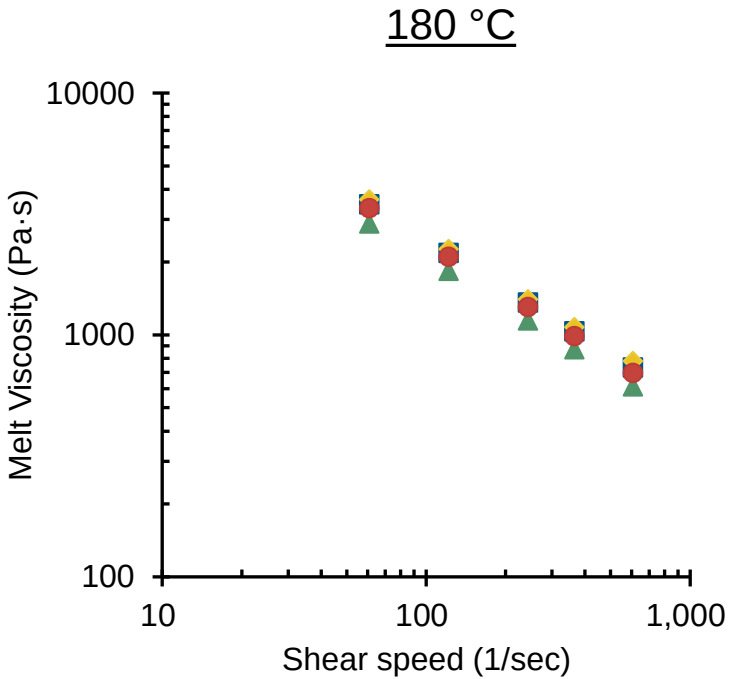
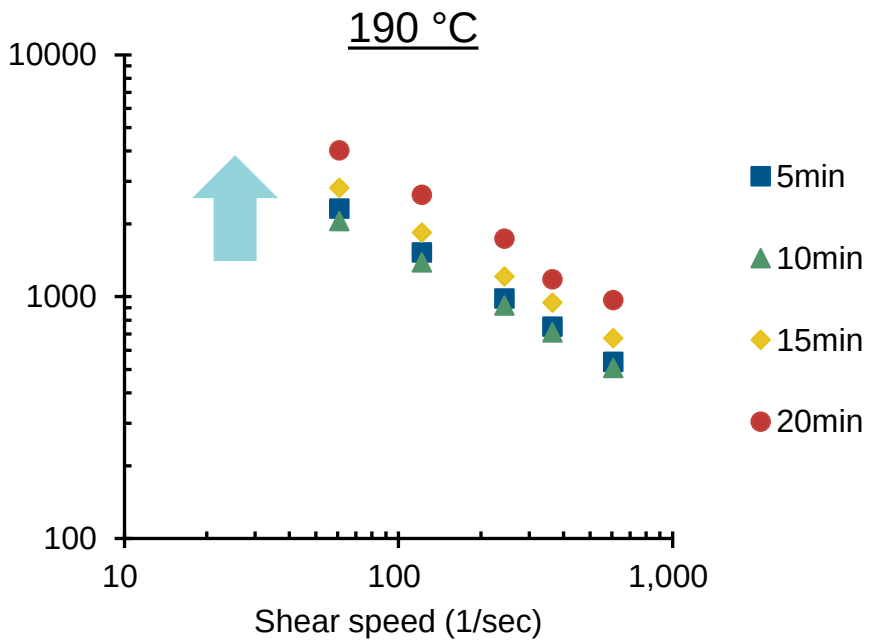
– At temperature upper than 190 °C, melt viscosity is increased due to the cross linkage of HPMCAS





Thermal Gravimetry

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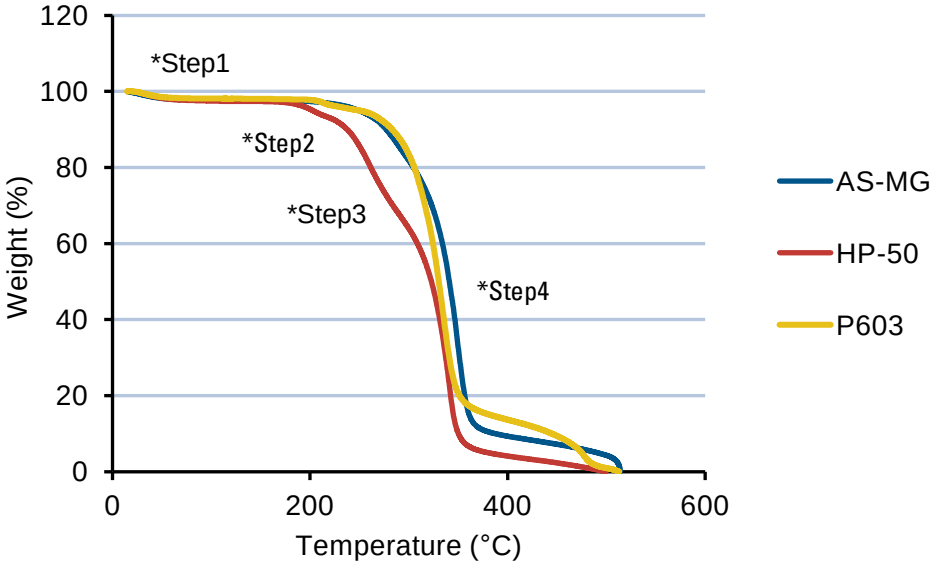
See the weight change in heating with heat analysis

– Evaporation, Degradation, Oxidation, Combustion



Degradation profile of cellulose derivatives

	Mechanism	Polymer
Step 1	Water evaporation	AS, HPMC, HP
Step 2	Chain structure degradation by Phthalic group	HP
Step 3	Evaporation of Phthalic anhydrate	HP
Step 4	Chain structure degradation	AS, HPMC, HP

Thermal Stability of HPMCAS by TGA

- Isothermal study showed that about 1.5-2.5% weight loss was observed when HPMCAS was maintained at 120C due to evaporation of moisture. While a final 4% weight loss attributed to the thermal degradation was detected when ramp heating to 260C.

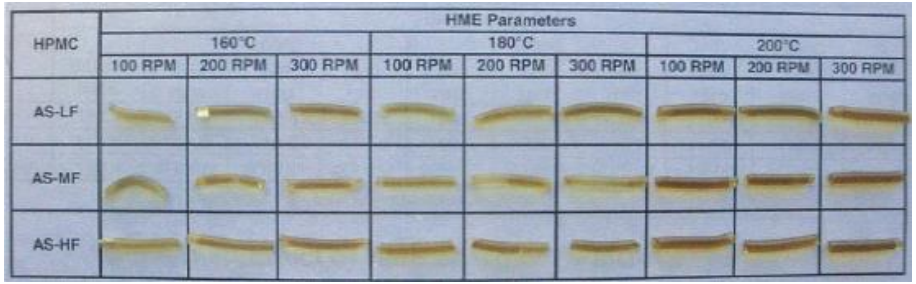
- The thermal degradation onset was found at 180C where the initial weight loss begins (approx. 0.1%). The total weight loss due to thermal degradation was about 0.07-0.3%. However, the period of the thermal stability part of measurement (8 min) was well above the typical residence time of HPMCAS within the extruders (5s-2 min).

- Therefore, HPMCAS can be thermally processed without significant risk of thermal degradation at melt temperatures of 170-180C.

Polymer Stability after Extrusion

(Shin-Etsu AQOAT only, Haake MiniLab®)

grade		viscosity	Loss on Drying	Substituent (%)				free acid (%)		Total acid (%)
AS-MF		cP		MeO	HPO	Ac	Suc	Succinic acid	Acetic acid	
Temp. (℃)	roter (rpm)									
before HME		2.76	1.3	23.0	7.2	9.3	11.4	0.03	0.04	0.07
160	100	2.66	1.3	22.9	7.1	9.4	11.1	0.44	0.10	0.53
	200	2.60	1.1	23.1	7.2	9.3	10.8	0.68	0.12	0.80
	300	2.60	1.1	23.0	7.1	9.4	10.7	0.85	0.14	1.00
180	100	2.62	1.2	23.0	7.3	9.2	10.8	0.72	0.11	0.82
	200	2.59	1.1	23.0	7.2	9.3	10.8	0.77	0.12	0.89
	300	2.59	1.1	23.1	7.2	9.3	10.9	0.88	0.12	1.00
200	100	2.50	1.1	23.0	7.2	9.2	10.4	1.19	0.16	1.35
	200	2.46	1.0	23.0	7.2	9.3	10.5	1.09	0.15	1.23
	300	2.50	1.2	23.0	7.2	9.1	10.1	1.13	0.16	1.29

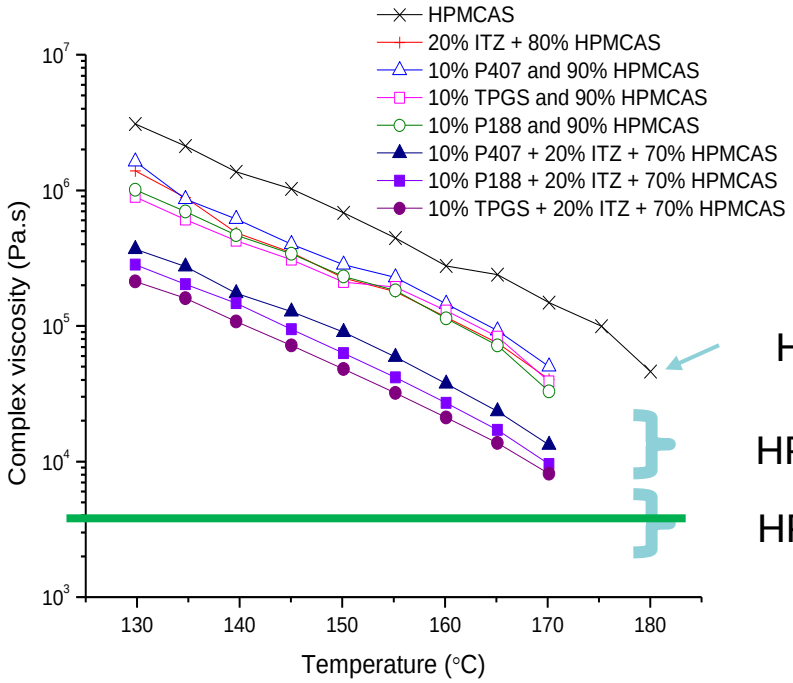


Cleavage of Succinoyl Groups

Polymer Stability after Extrusion

- Polymer undergo degradation based on two types of chemical reactions, the main chain reactions and the side chain reactions, respectively. The former include chain scission and cross-linking, whereas the latter comprises the elimination and /or cyclization of the side chain.
- Because of thermal and mechanical stresses imparted on the polymer by HME process, HPMCAS can undergo side chain elimination through hydrolysis, resulting in free acetic acid and succinic acid. The acidic impurities can react with hydroxyl groups of the APIs by esterification, affecting the quality of the final products.
- It has been reported that the free acids released are proportional to the screw speed at lower processing temperatures (160C), whereas free acid generation is not correlated with screw speed higher processing temperatures (200C).
- Therefore, it is necessary to select the HME process conditions carefully to inhibit or reduce the degradation.

Effect of Surfactant and Drug-Surfactant Mixture on Viscosity



HPMCAS

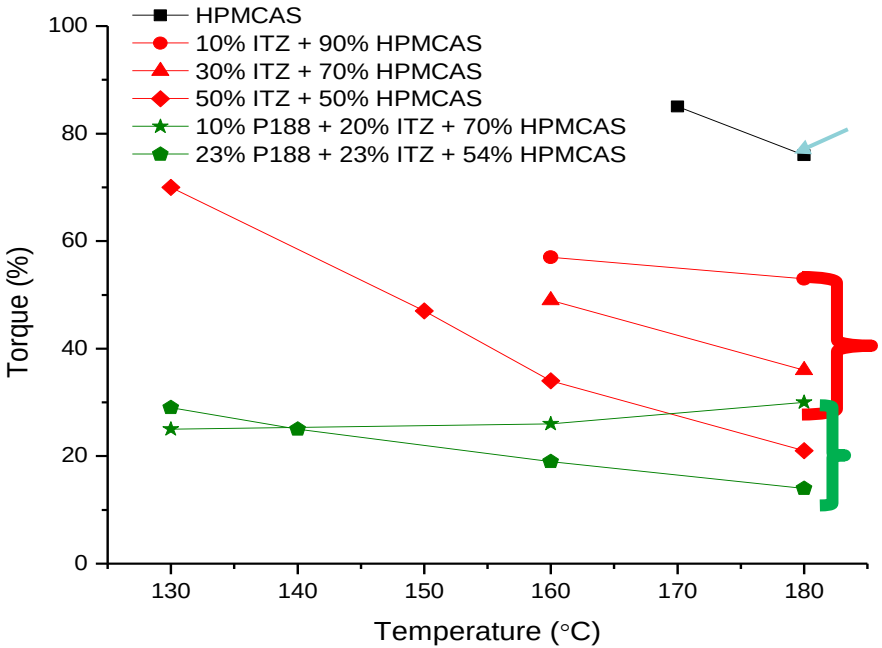
HPMCAS + **Surfactant**

HPMCAS + **Itraconazole** + **Surfactant**

Extrudable range: 1,000 to 10,000 Pa.s at angular frequency of 0.1 rad/sec

- HPMCAS exhibits high viscosity and only extrudable ≥170˚C by itself
- Addition of surfactant and/or itraconazole reduced viscosity of HPMCAS greatly

Extrudability of Drug-HPMCAS and Drug-Poloxamer 188-HPMCAS mixtures at 130 and 170˚C (with Drug)



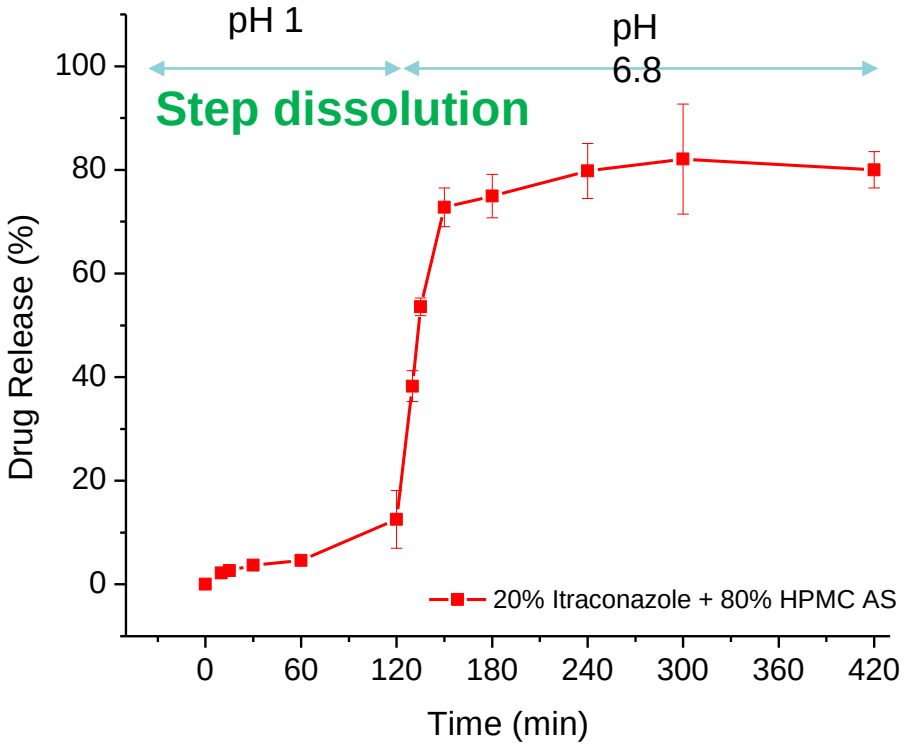
HPMCAS

HPMCAS + **Itraconazole**

HPMCAS + **Itraconazole** + **P188**

- Itraconazole-HPMCAS and Itraconazole-Poloxamer 188-HPMCAS were extruded at 130˚C, and drug was converted to amorphous form
- Milled filaments were exposed to 40C/75% RH for a month and found to be physically stable by DSC and no separation or crystallization was observed

Challenge: Drug Release from Milled Extrudates of Itraconazole-HPMCAS ASD

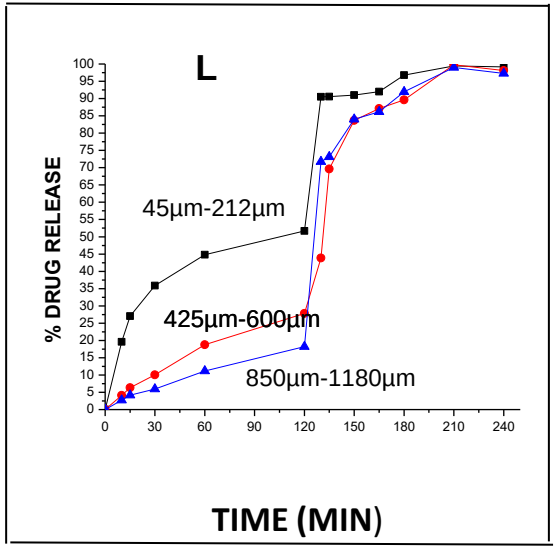


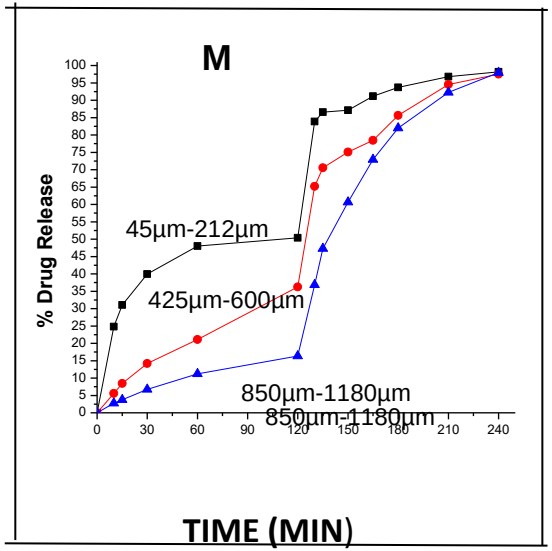
Step dissolution (2 h at pH 1 and 5 h at pH 6.8)

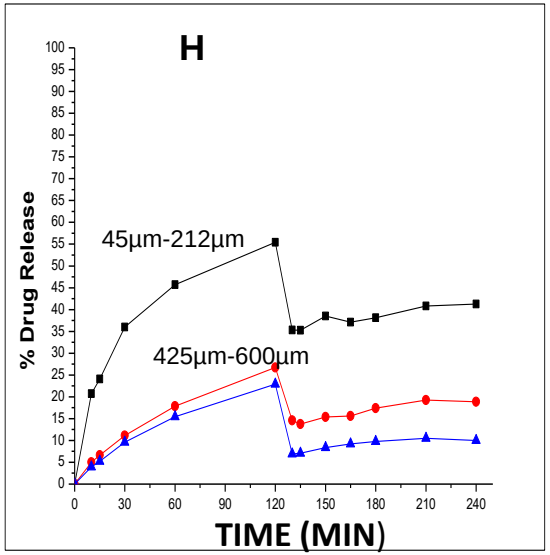
- **Low** drug release at pH 1
- **Incomplete** drug release upon changing pH to 6.8

- Drug release from milled extrudates containing 100 mg itraconazole in 250 mL of dissolution medium using dissolution Apparatus II at 75 rpm

Drug Release from Milled Extrudates (Surfactant: P407)







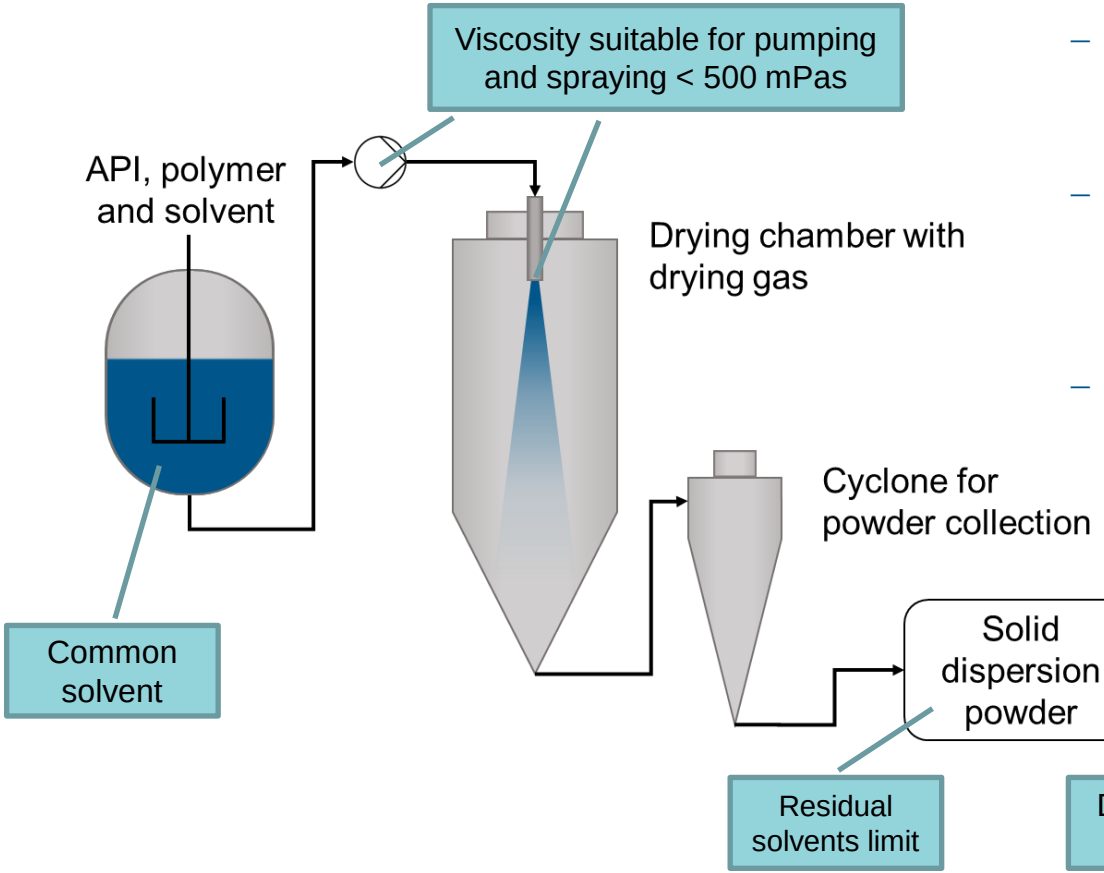
20% ITZ+15% P407+ 65%HPMCAS-LG (45µm-212µm)
20% ITZ+15% P407+ 65%HPMCAS-LG (425µm-600µm)
20% ITZ+ 15% P407+ 65% HPMCAS-LG (850µm-1180mm)

20% ITZ+15% P407+ 65%%HPMCAS-MG (45µm-212µm)
20% ITZ+15% P407+ 65% HPMCAS-MG (425µm-600µm)
20% ITZ+15% P407+ 65% HPMCAS-MG (850µm-1180mm)

20% ITZ+15% P407+ 65% HPMCAS-HG (45µm-212µm)
20% ITZ+15% P407+ 65% HPMCAS-HG (425µm-600µm)
20% ITZ+15% P407+ 65% HPMCAS-HG (850µm-1180mm)

- Drug release from **milled extrudates** containing 100 mg itraconazole in 250 mL of dissolution medium using dissolution Apparatus II at 75 rpm

Spray Drying



- When?
  - High melting point API
  - Solubility of API in organic solvent
- Requirements?
  - Common organic solvent for API and carrier polymer
  - Low viscosity of spray solution
- Spray Dried Powder?
  - Small particle size
  - Low bulk density
  - Residual organic solvents → post-drying
  - Downstream processing required

Solubility of Cellulose Derivatives

Experiment

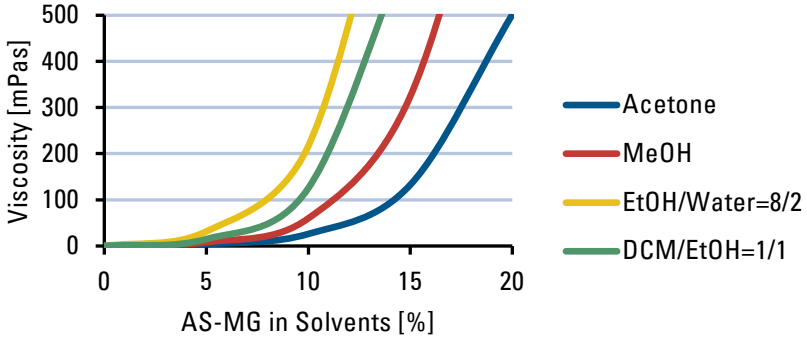
Cellulose derivatives were dissolved into various organic solvents. The polymer content was 5% and the solvents were mixed by weight ratio at room temperature. After stirring, the mixture was stood still for a day, then the solubility was judged by visual.

CS: Clearly soluble (solution may be slightly opaque), S: Soluble (Haze) P: Partly soluble or swelling, I: Insoluble

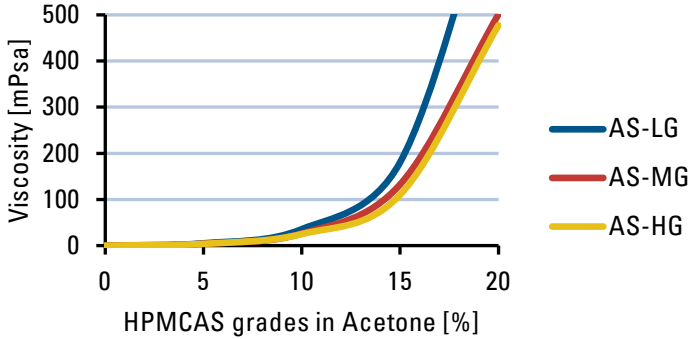
	HPMC 2910	HPMC 2906	HPMC 2208	MC	HPMCP		HPMCAS		
	PHARMACOAT® 603	–	SB-4	METOLOSE® SM-4	HP-50	HP-55	AS-LG	AS-MG	AS-HG
Water	CS	CS	CS	CS	I	I	I	I	I
Methanol (MeOH)	P	I	I	I	I	P	S	S	S
Water/MeOH (5/5)	CS	CS	CS	S	P	P	P	P	P
Ethanol (EtOH)	I	I	I	I	I	P	P	P	P
Water/EtOH (2/8)	CS	S	S	S	CS	CS	S	S	S
Water/EtOH (5/5)	CS	CS	CS	S	P	P	S	S	S
Water/EtOH (6/4)	CS	CS	CS	CS	P	P	I	I	I
Isopropyl alcohol (IPA)	I	I	I	I	I	I	P	P	P
Water/IPA (2/8)	CS	S	S	S	CS	S	S	S	S
Water/IPA (5/5)	CS	CS	CS	S	P	P	S	S	S
Acetone	I	I	I	I	I	S	S	S	S
Water/Acetone (5/5)	CS	CS	CS	S	P	P	P	P	P

	HPMC 2910	HPMC 2906	HPMC 2208	MC	HPMCP		HPMCAS		
	PHARMACOAT® 603	–	SB-4	METOLOSE® SM-4	HP-50	HP-55	AS-LG	AS-MG	AS-HG
Diethyl ether	I	I	I	I	I	I	I	I	I
Ethyl acetate	I	I	I	I	I	P	S	S	S
Methyl acetate	I	I	I	I	I	S	S	S	S
Acetic acid	CS	S	S	S	CS	CS	S	S	S
Dichloromethane (CH_2Cl_2)	P	P	P	P	P	P	P	P	S
CH_2Cl_2/MeOH (5/5)	CS	CS	S	S	CS	CS	S	S	S
CH_2Cl_2/EtOH (5/5)	CS	S	S	S	CS	CS	S	S	S
CH_2Cl_2/IPA (5/5)	S	S	S	S	CS	CS	S	S	S
Benzyl alcohol	CS	CS	CS	CS	CS	CS	CS	CS	CS
Dimethyl sulfoxide (DMSO)	CS	CS	CS	CS	CS	CS	CS	CS	CS
N-Methylpyrrolidone (NMP)	CS	CS	CS	CS	CS	CS	CS	CS	CS
Tetrahydrofuran (THF)	I	I	I	I	CS	CS	S	S	S
N,N-Dimethylformamide (DMF)	CS	CS	CS	S	CS	CS	CS	CS	S
N,N-Dimethylacetamide (DMA)	CS	CS	CS	S	CS	CS	CS	CS	CS
Toluene	I	I	I	I	I	I	P	P	P
1,4-Dioxane	I	P	I	I	CS	CS	S	S	S
Sodium hydrogen carbonate (1%)	CS	CS	CS	S	CS	CS	CS	CS	S
NaOH (0.5%)	CS	CS	CS	CS	CS	CS	CS	CS	CS
NH_4OH (0.96%)	CS	CS	CS	CS	P	P	P	CS	CS

HPMCAS in Organic Solvents

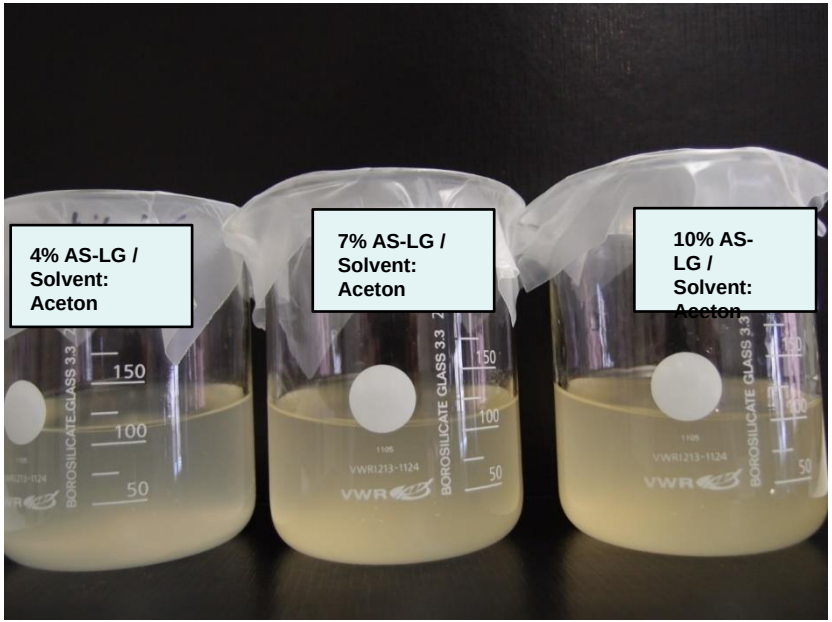


- Wide range of solvent is applicable
- Viscosity differs from solvent used
  - Low viscosity preferred (< 500 mPas)
  - EtOH/water > DCM/EtOH > MeOH > Acetone



- Viscosity slightly depending on AS grade
  - AS-LG gives slightly higher viscosity
  - No difference AS-MG and AS-HG

Spray Drying



Spray Drying

Formulation and conditions for spray drying trial:

HPMCAS-LG: Felodipine 3:1 Solvent, Acetone

Felodipine was dissolved in acetone and the HPMCAS was added slowly and mixed for one hour.

GEA Niro 12.5CC pilot plant

Equipped with 4 pneumatic hammers, HEPA filters & Cyclone to collect the primary powder fraction.

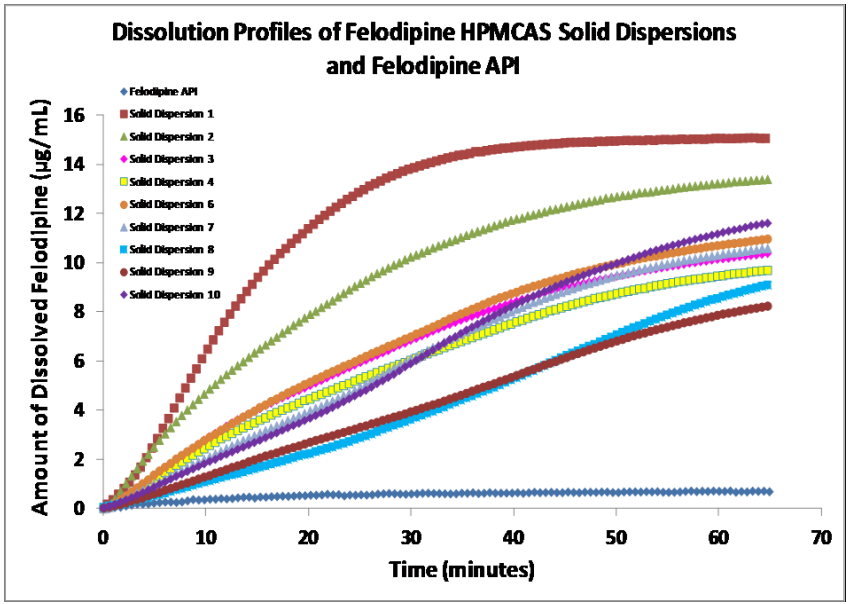
Including the controlled room

Post drying was needed as LOD >2%. LOD after drying around 1%

Spray Drying

Test Number	Trial Temp(0C)		Nozzle	Solid content	Pressure	Feed Rate	Particle Size	LOD	Quantity	Bulk density (g/ml)	
	Inlet	Outlet	(mm)	(%)	(bar)	(kg/hr)	D50 (um)	(%)	(kg)	Lose	Tap
1	**68**	**50**	**0.71**	**5**	**55**	**25**	**14**	**3.2**	**0.50**	**0.21**	**0.36**
2	64	49	0.71	5	18	15	27	2.7	0.50	0.20	0.26
3	66	49	0.78	10	16	23	49	3.52	0.60	0.19	0.25
4	**68**	**49**	**0.98**	**10**	**13**	**25**	**50**	**2.79**	**0.65**	**0.19**	**0.27**
5	49	38	0.98	10	13	25	47	3.43	0.65	0.19	0.27
6	70	41	1.18	10	9	45	71	3.98	0.90	0.20	0.28
7	100	44	1.18	10	60	100	44	3.28	1.00	0.20	0.30
8	**60**	**41**	**1.18**	**12.4**	**12**	**45**	**115**	**4.54**	**1.20**	**0.19**	**0.28**
9	65	35	1.18	12.4	32	69	94	5.32	0.80	0.20	0.29
10	101	42	1.18	12.4	68	128	61	3.4	1.30	0.24	0.34

Spray Drying



Dissolution profile was dependant on particle size. Fine particles fluffy material

Summary

- AQOAT® can easily be spray dried as amorphous dispersion due to very low viscosity
- Solution is turbid due to HPMC backbone
- Dissolution profile can be modified by dropplet size
- Downstreaming considerations
  - Particles distribution
  - Compressibility

Thank you for your attention

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