Double Action of HPMCAS as a Binder and Precipitation inhibitor in ASD tablets prepared by hot melt extrusion.

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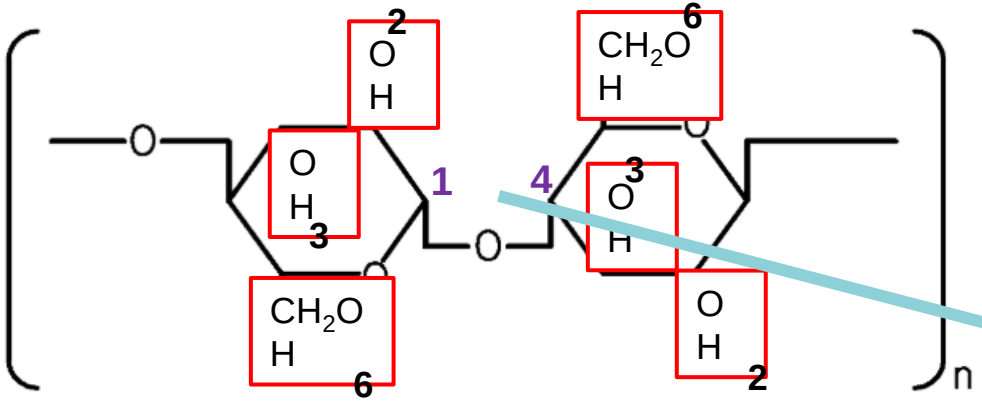
Hydroxypropyl Methylcellulose (HPMC)



Cellulose

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

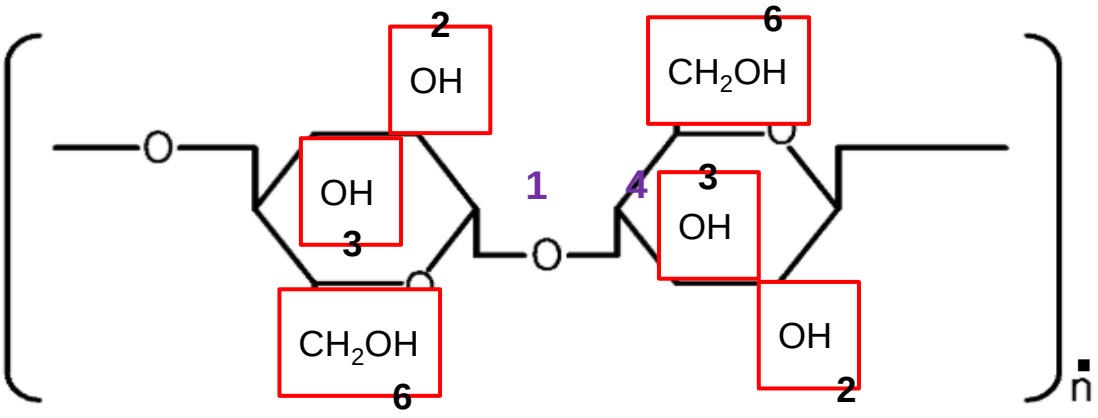
Anhydroglucose units
With 1,4 β glyosidic bond

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

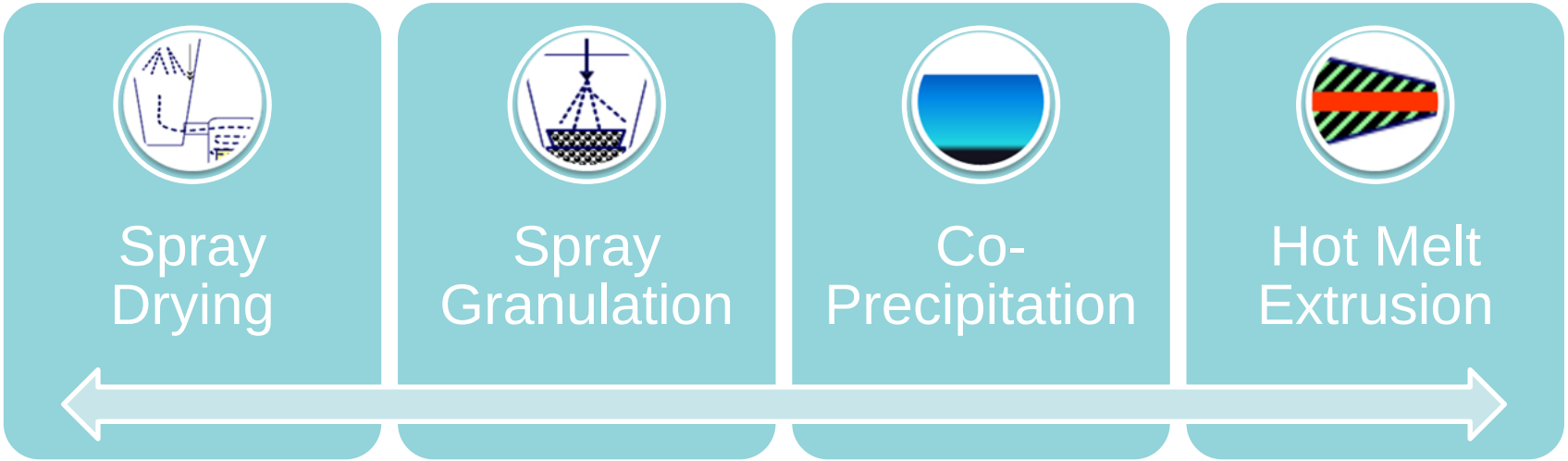
Substitution	Chemical Composition
Me	-CH_3
HP	-$CH_2CH(CH_3)OH$
HPMe	-$CH_2CH(CH_3)OCH_3$
Ac	-$COCH_3$
Su	-$COCH_2CH_2COOH$
HPAc	-$CH_2CH(CH_3)OCOCH_3$
HPSu	-$CH_2CH(CH_3)OCOCH_2CH_2COOH$

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).

Commercial Products Using HPMCAS (Mainly US)

Year Approved	Product Name	API	Supplier/Manufacturer	Dosage Form
2001	Prozac Weekly	Fluoxetine HCL	Eli Lilly	Beads in Capsule
2004	Cymbalta	Duloxetine HCL	Eli Lilly	Beads in Capsule
2008	Omeprazole (OTC)	Omeprazole	Dexcel Pharma (Isreal)	Tablet
2010	Tamsulosin HCL	Tamsulosin HCL	Sun Pharma (India)	Beads in Capsule
2011	Diethylpropion ER	Diethylpropion	Adiarex Pharma	Tablet
2011	Zelboraf	Vemurafenib	Roche	Tablet
2012	Kalydeco	Ivacaftor	Vertex	Tablet
2013	Noxafil Tablet	Posaconazole	Merck	Tablet
2013	Methylphenidate HCL	Methylphenidate HCL	Kremars Urban/Actavis	Tablet
2014	Mycophenalic Acid	Mycophenalic Acid	Mylan	Tablet
2014	Dexamethylphenidate HCL	Dexamethylphenidate HCL	Catalent / Impass	Beads in Capsule
2015 (EU)	Simparica	Sarolaner	Zoetis (Belgium)	Chewable Tablet
2015	Orkambi	Lumacaftor-Ivacaftor	Vertex	Tablet
2016	Moxatag	Amoxacillin	SUIR (Ireland) / Vernalis	Tablet
2017	Idhifa	Enasidenib Mesylate	Agios/Celgene	Tablet
2018	Methylphenidate HCL (LA)	Methylphenidate HCL	Catalent / Teva	Beads in Capsule
2018	Symdeco	Tezacaftor-Ivacaftor	Vertex	Tablet
2018	Erleada	Apalutamide	Janssen	Tablet
2018	Tibsovo	Ivosidenib	Agios	Tablet
2018 (JP/EU)	Xtandi	Enzalutamide	Astellas	Tablet
2018	Delstrigo	Doravirine-Lamivudine-Tenofovir	Merck	Tablet
2018	Pifeltro	Doravirine	Merck	Tablet
2019	Posaconazole Tablet	Posaconazole	Generic	Tablet
2019	Cyclobenzaprine Capsule	Cyclobenzaprine HCL	Apotex	Beads in Capsule
2020	Qinlock	Ripretinib	deciphera	Tablet
2021	Ferriprox	Deferiprone	Chiesi	Tablet
2021	Welireg	Belzutifen	Merck	Tablet
2022	Sotyktu	Deucravacitinib	BMS	Tablet
2023	Japirca	Pirtibrutinib	Lily	Tablet
2024	Voydeya	Danicopan	AstraZeneca (Alexion)	Tablet

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%

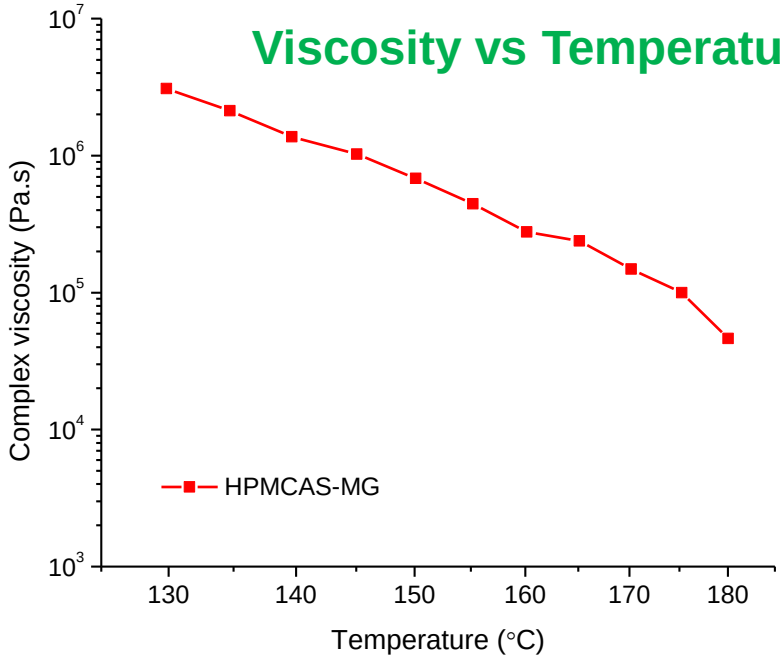
- The succinate groups has a pKa of about 5, and therefore, the polymer is less than 10% ionized at pH values below about 4 and is at least 50% ionized at pH values of about 5 or higher.
- Due to the presence of relatively hydrophobic methoxy and acetate substituents, HPMCAS is water insoluble when unionized (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

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.

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.

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

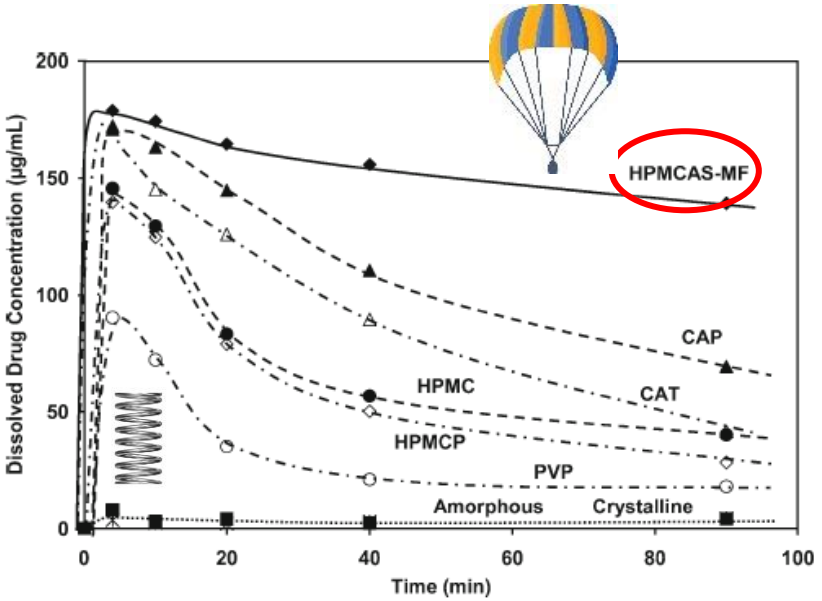
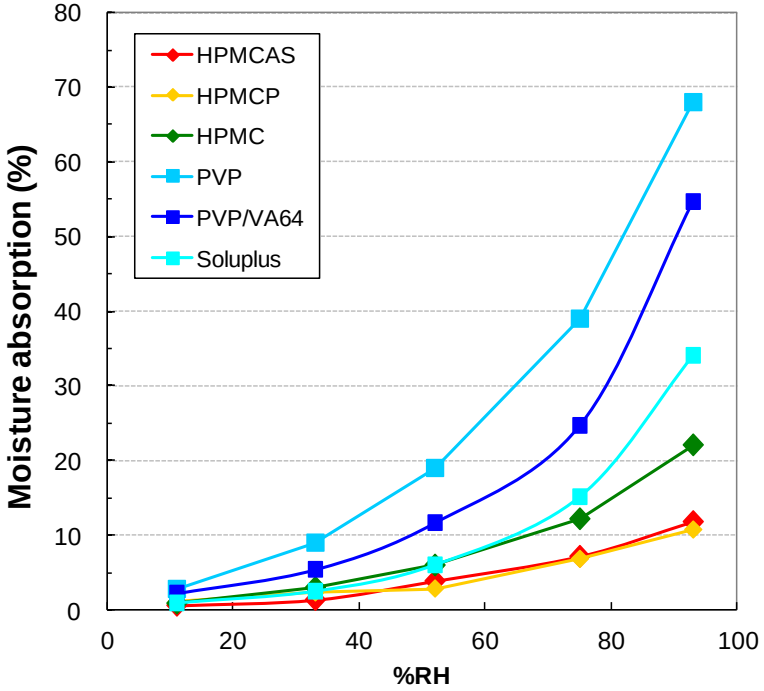


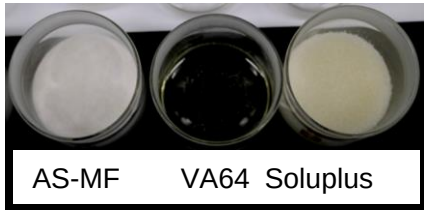
Fig. 7. Dissolution performance of SDDs made with Compound 5 and various polymers, at 10% drug loading. Dissolution was carried out using the microcentrifuge dissolution test in PBS at 37°C, with a 200 µg/ml total concentration (dissolved plus undissolved drug).

*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.

Equilibrium Moisture Content



93%RH, 30days



PVP-based polymers are very hygroscopic.

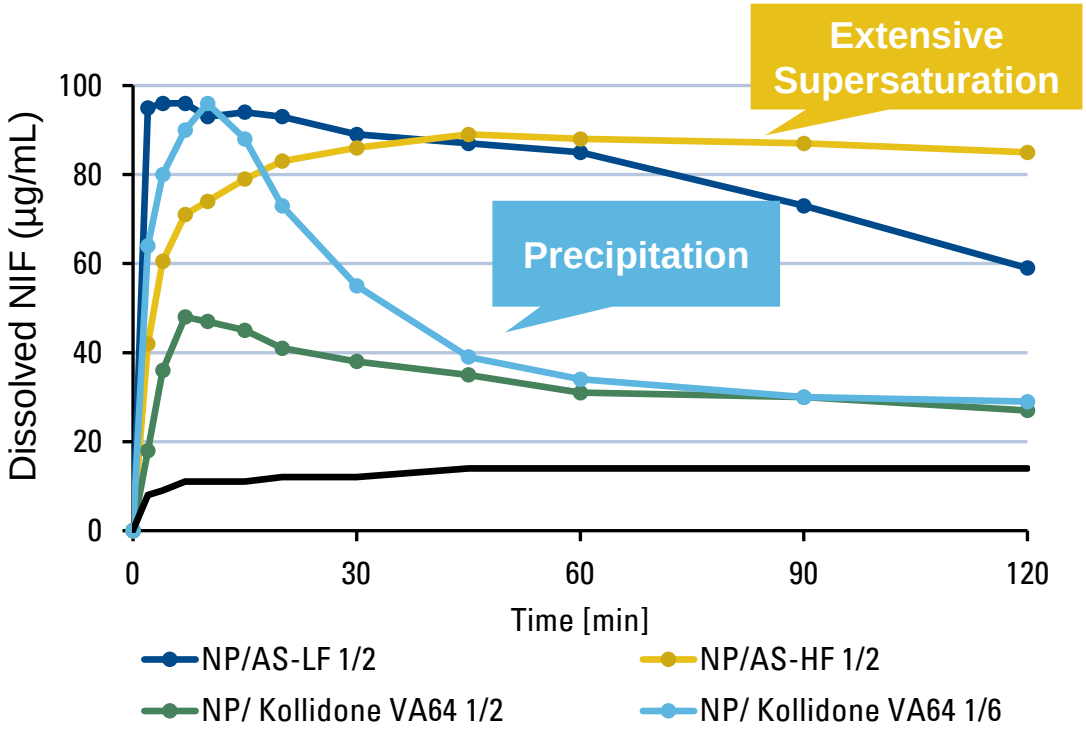
・Soluplus swells at high moisture

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.

HPMCAS-HF extends supersaturation phase and inhibits precipitation



- **Precipitation** might occur depending on API:Polymer combination
- A high solubility of the API in the polymer will not always results in stabilization of supersaturation
- **HPMCAS (specially H-grade)** show extension of supersaturation)

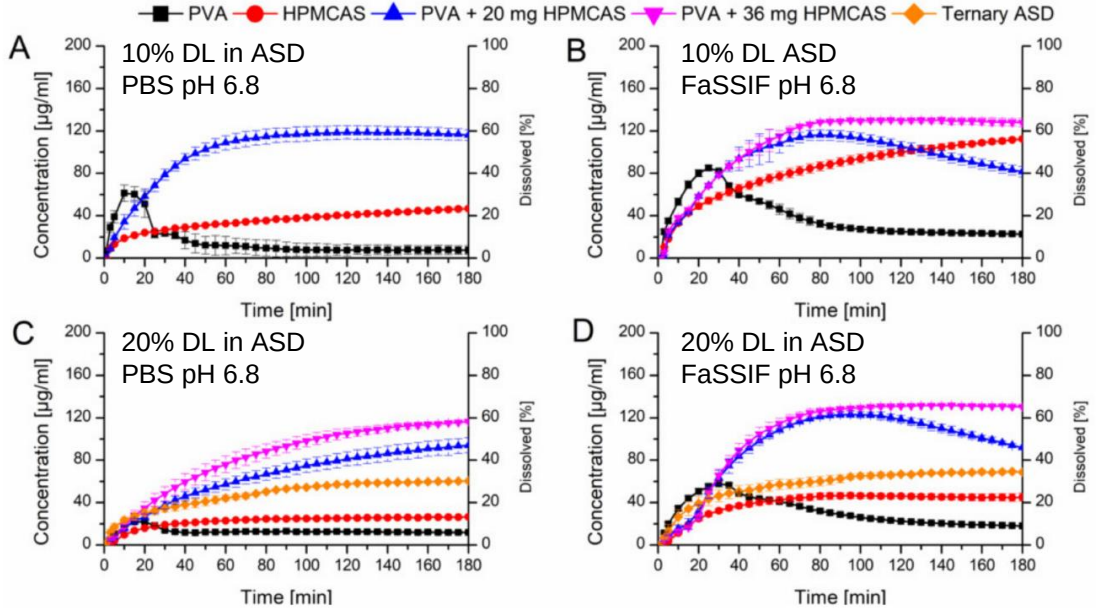
ASDs extruded @ MiniLab @ 170 °C, 20 rpm. Milled after extrusion. ASD equivalent of 100 mg Nifedipine dissolved in buffer pH 6.8

Precipitation Inhibition of HPMCAS

HPMCAS extended the supersaturatoin state (prevented precipitation) of Celecoxib from PVA ASD

- **F1: ASD of Celecoxib:PVA**
- **F2: ASD of Celecoxib:HPMCAS**
- **F3: ASD of Celecoxib:PVA + 20 mg HPMCAS (in solution)**
- **F4: ASD of Celecoxib:PVA + 36 mg HPMCAS (in solution)**
- **F5: Ternary ASD (20% PVA ASD + 36 mg HPMCAS) extruded together.**

Adding HPMCAS to dissolution medium prevented precipitation of Celecoxib from PVA ASDs



Reproduced from reference figure 8: Monophasic non-sink dissolution studies of plain ASDs and of PVA ASDs with admixed HPMCAS powder at a drug load of 10% in PBS at pH 6.8 (A), in FaSSIF at pH 6.8 (B), at a drug load of 20%, including ternary ASD in PBS at pH 6.8 (C) and in FaSSIF at pH 6.8 (D). MiniDissolution apparatus (paddles 20 mL, 37 °C, 75 rpm).

Monschke, M.; Wagner, K.G. *Pharmaceutics* **2020**, *12*, 1–17, doi:10.3390/pharmaceutics12060541.

HPMCAS improves the dissolution of High load dosage form (HLDF) Erloitinib: Eudragit L-100 ASD

- HLDF Erolitinib:Eudragit L100 were prepared by spray drying. (Lower tablet weight)

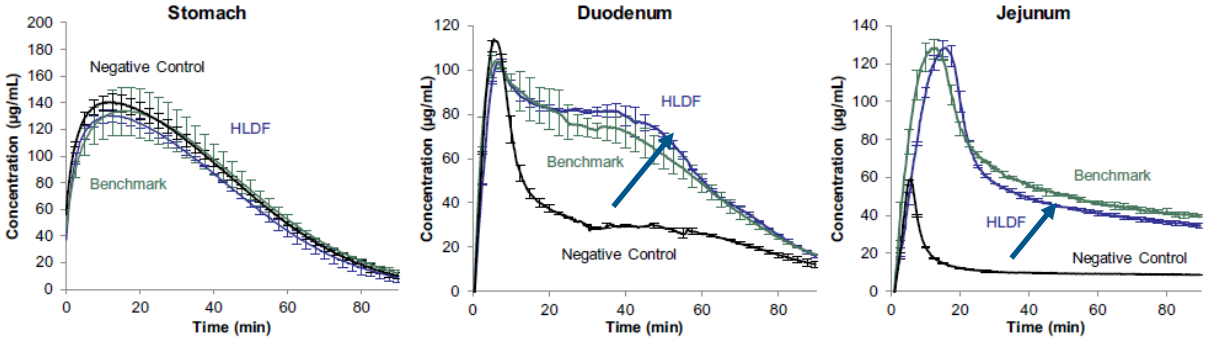
HPMCAS-HF was added in RC step in HLDF formulation

Tablet formulation [a]	% Drug loading in tablet	Tablet mass (mg)	ASD composition	% ASD in tablet	% External HPMCAS-H in tablet	% Tableting excipients in tablet [b]
HLDF	29	350	65/35 erlotinib/Eudragit L100	44	29	27
Benchmark	18	575	35/65 erlotinib/HPMCAS-H	50	0	50
Negative control	29	350	65/35 erlotinib/Eudragit L100	44	0	56

[a] The majority of excipients (including external HPMCAS-H for the HLDF tablet) are granulated with the ASD. Additional excipients are blended with the granules and the final blend is compressed into tablets. Detailed compositions can be found in Table A.1. in appendix section A.1.
[b] Tableting excipients include Avicel PH 101, lactose monohydrate 310, ac-di-sol, cab-o-sil M5P and magnesium stearate.

Adding HPMCAS in RC step to Erlotinib:Eudragit ASD increases the dissolution AUC in HLDF formulation

Negative control (*no HPMCAS-HF added in RC step*) ----- HLDF (*HPMCAS-HF added in RC step*)



Reproduced from figure 5 of the publication: Concentration time profiles in the stomach, duodenum and jejunum compartments of the Controlled Transfer Dissolution (CTD) test at low (pH 2) gastric pH.

Mudie, D.M.; Buchanan, S.; Stewart, A.M.; Smith, A.; Shepard, K.B.; Biswas, N.; Marshall, D.; Ekdahl, A.; Pluntze, A.; Craig, C.D.; et al. *Int. J. Pharm. X* **2020**, *2*, 100042, doi:10.1016/j.ijpx.2020.100042.

A binder is necessary to use in ASD tablet formulations prepared by HME

- ASD extrudates are usually difficult to compact into tablets

- Tablet binders are necessary to use to ensure good compactibility and tensile strength of ASD tablets

Double action of HPMCAS as PI and Binder in ASD tablets prepared by HME

Goal of the study: Establishing the double action of HPMCAS as a precipitation inhibitor and binder in ASD tabets prepared by HME

Formulations:

2 ASD polymeric carriers were used (HPMCAS-LMP) vs (PVPVA (Kollidon® VA-64)

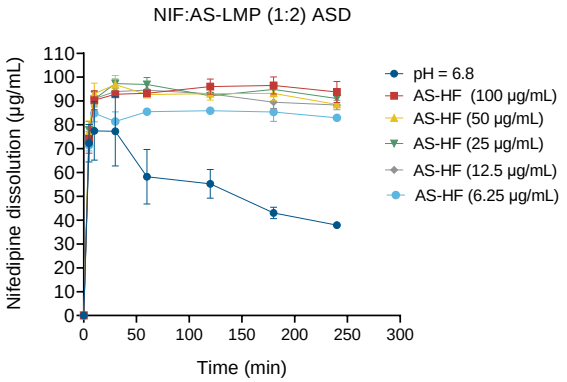
- **Nifedipine:AS-LMP (1:2)** ASD prepared by HME
- **Nifedipine:VA-64 (1:2)** ASD prepared by HME
- **Nifedipine:VA-64 (1:6)** ASD prepared by HME
- Dose of Nifedipine = 100 µg/ml

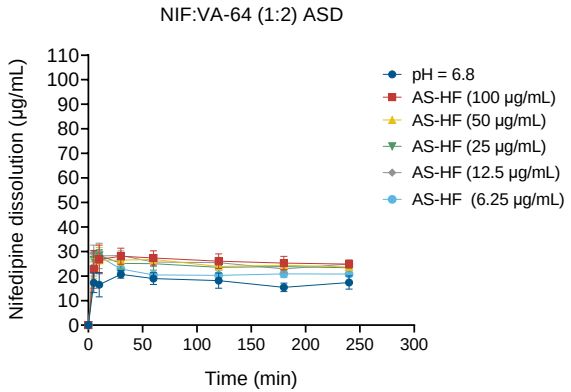
Methods

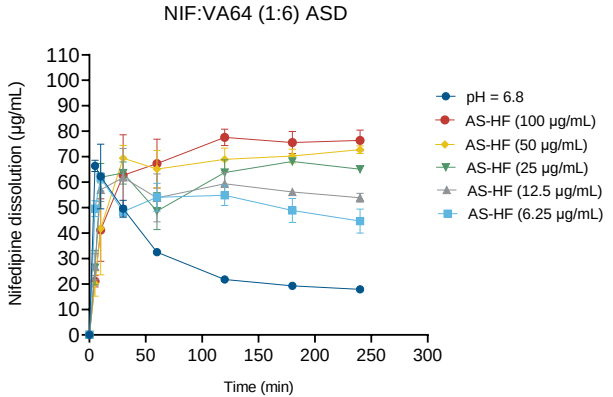
- NIF ASD formulations (1:2) AS:LMP and (1:2 and 1:6) VA64 with HME
- In vitro release studies
- ASD characterization (SEM, particle size, DSC)
- ASD tablet formulations
- Tablet properties and tablet compaction studies
- Tablet dissolution studies

In vitro dissolution studies of NIF ASD milled extrudates

1- AS-LMP as an ASD carrier enhances the dissolution of NIF in comparison to PVPVA-VA64
2- Independent of the carrier polymer, **AS-HF acts as a precipitation inhibitor**



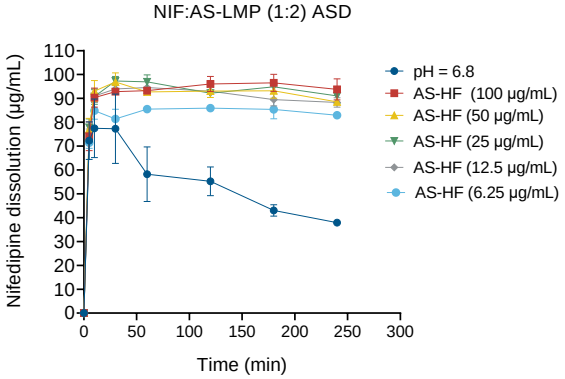


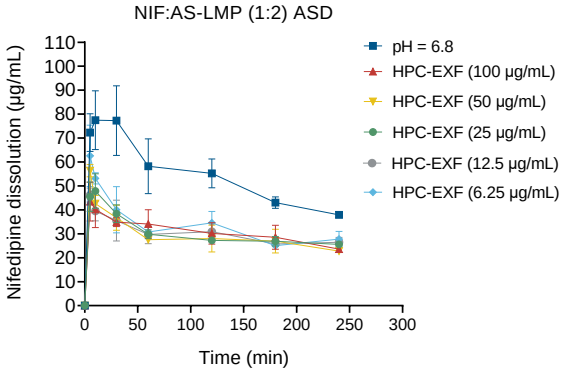


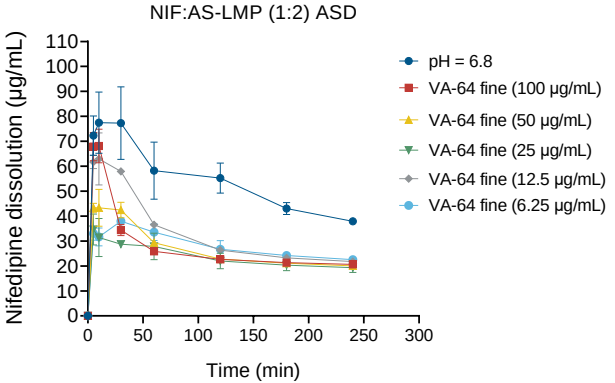
In vitro dissolution studies of NIF ASD milled extrudates

Independent of ASD carrier polymer, AS-HF acts as a precipitation inhibitor in comparison to commonly used dry binders (HPC-EXF and VA64 fine)

1- **AS-LMP** as ASD carrier polymer (AS-HF vs HPC-EXF vs VA64 fine as PI)



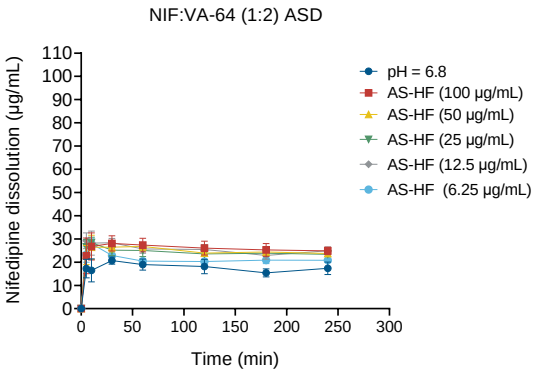


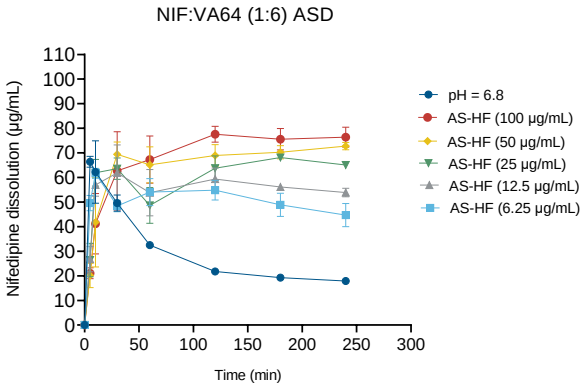


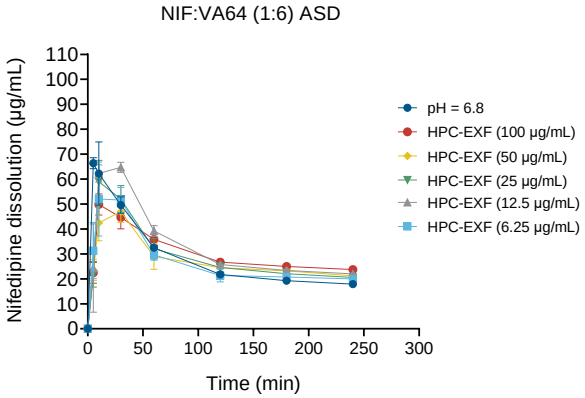
In vitro dissolution studies of NIF ASD milled extrudates

Independent of ASD carrier polymer, AS-HF acts as a precipitation inhibitor in comparison to commonly used dry binders (HPC-EXF and VA64 fine)

2- VA-64 as ASD carrier polymer (AS-HF vs HPC-EXF as PI)





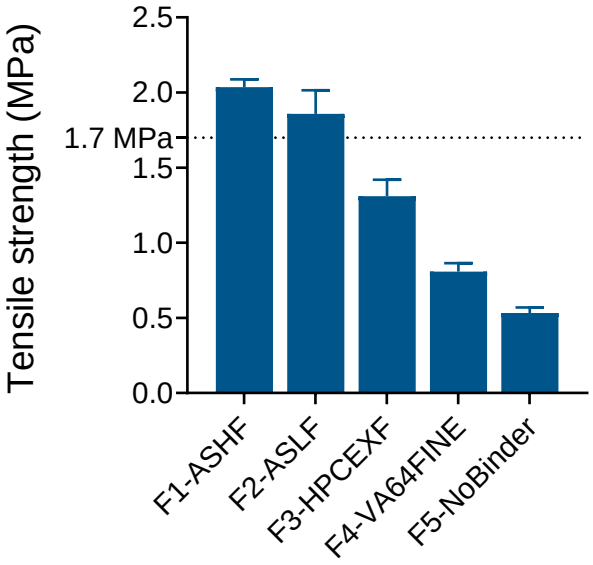


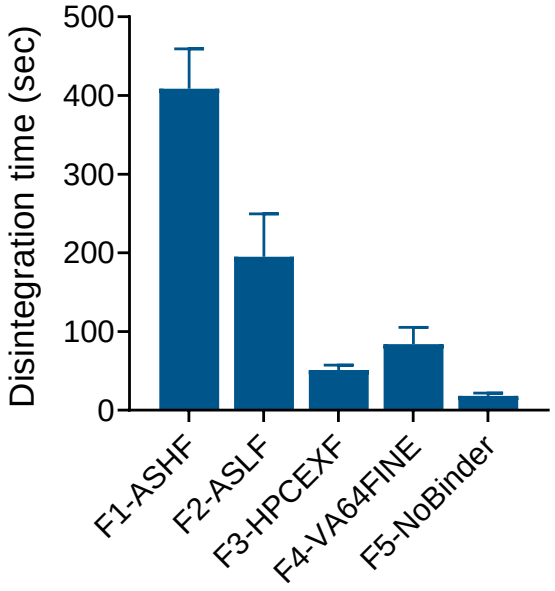
ASD tablet formulations

Material	Function	F1-ASHF (w/w %)	F2-ASLF (w/w %)	F3-HPCEXF (w/w %)	F4-VA64FINE (w/w %)	F5-NoBinder (w/w %)
NIF:AS-LMP (1:2)	ASD	65	65	65	65	65
AS-HF	Binder/PI	5	-	-	-	-
AS-LF	Binder/PI	-	5	-	-	-
HPC-EXF	Binder	-	-	5	-	-
VA64-Fine	Binder	-	-	-	5	-
Ac-Di-Sol	Disintegrant	10	10	10	10	10
MCC PH 102	Diluent	19.5	19.5	19.5	19.5	19.5
Mg Stearate	Lubricant	0.5	0.5	0.5	0.5	0.5

Compaction pressure = 147.57 MPa, **Tablet weight** = 400 mg, **Diameter** = 10 mm curved face (biconvex)

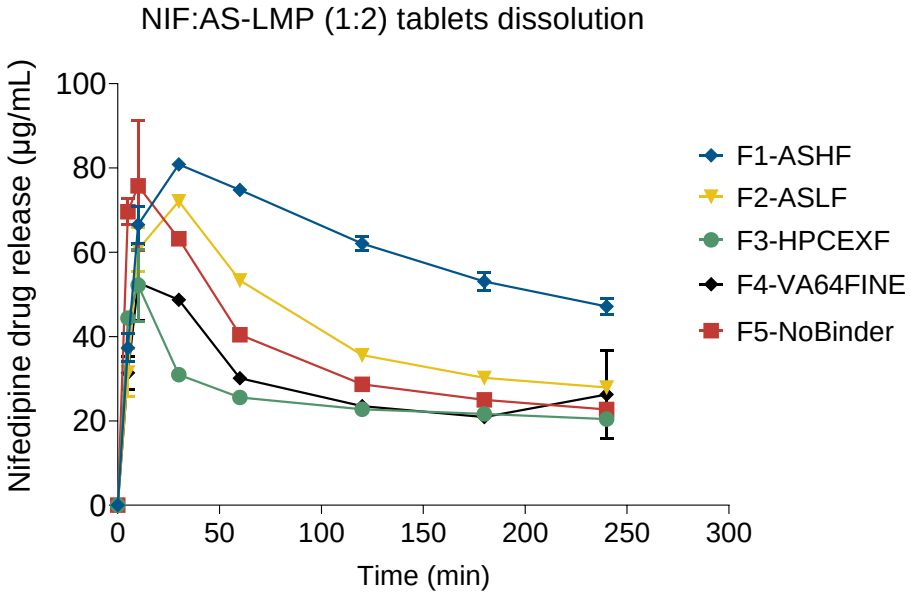
Tablet properties: Tensile strength – Disintegration time

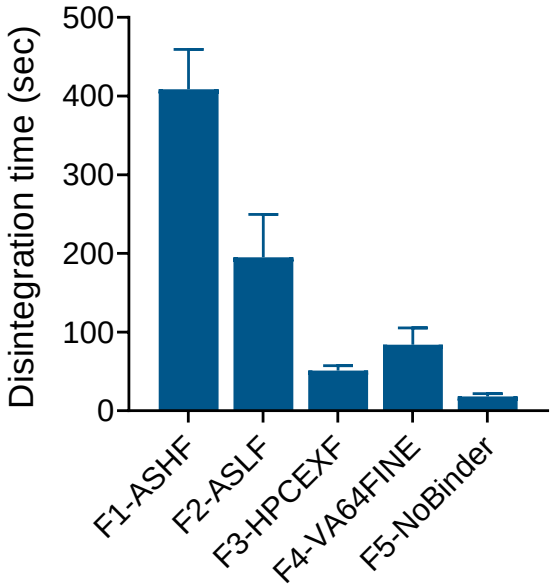




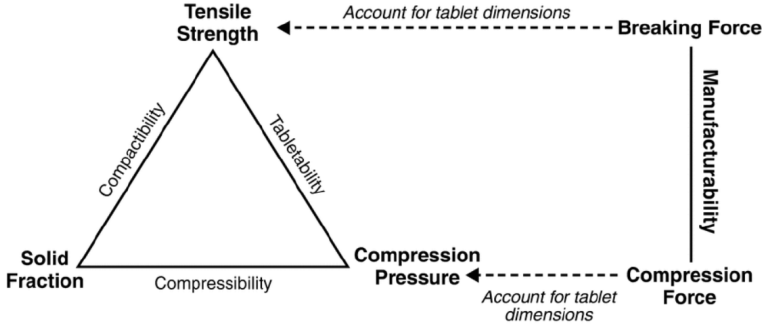
5% of ASHF/ASLF/HPCEXF/VA64FINE was used

NIF:AS-LMP (1:2) tablets in vitro dissolution studies





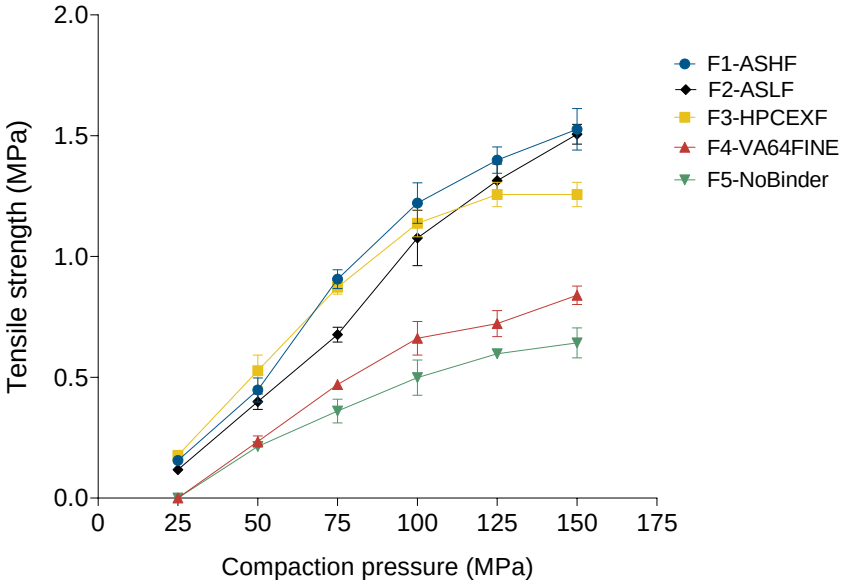
Compaction analysis



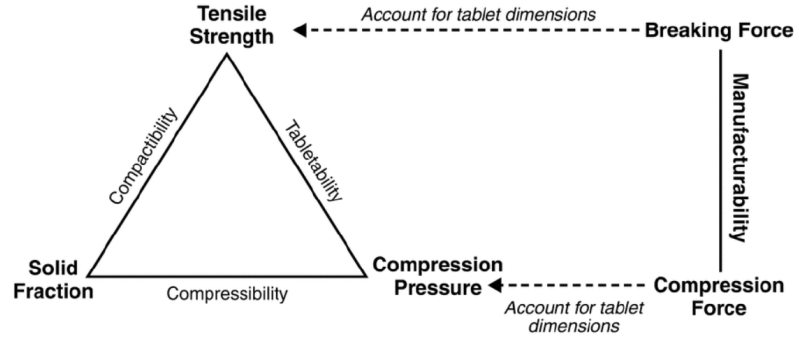
USP/NF ⟨1062⟩ TABLET COMPRESSION CHARACTERIZATION (25.08.2020)

Formulation	%
NDP:AS-LMP (1:2)	65%
AS-HF or AS-LF or HPC-EXF or VA-64 fine or 0%	5%
MCC-PH-102 (24.5% when 0% binder is used)	19.5%
Ac-Di-Sol	10%
Mag. Stearate	0.5%
Weight (mg)	400
Diameter (mm)	10

Tabletability profile

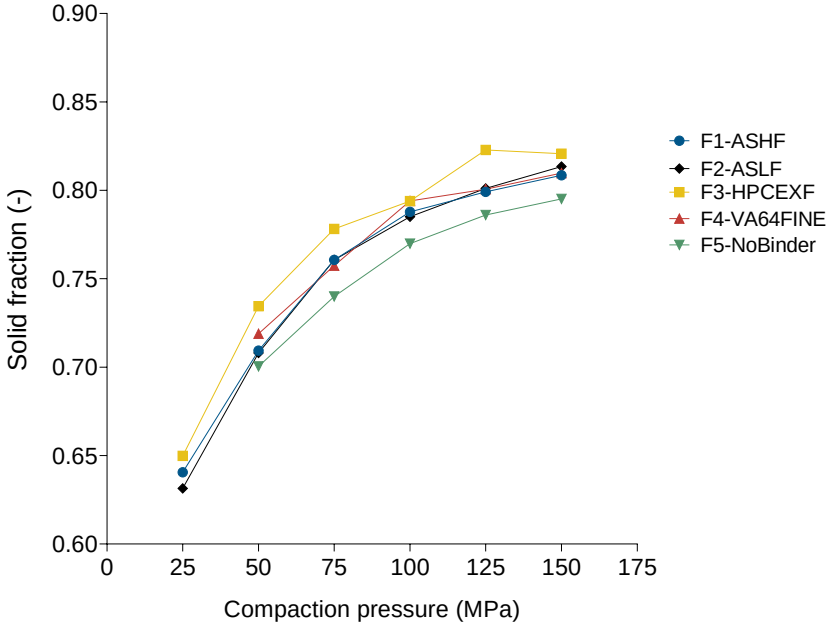


Compaction analysis

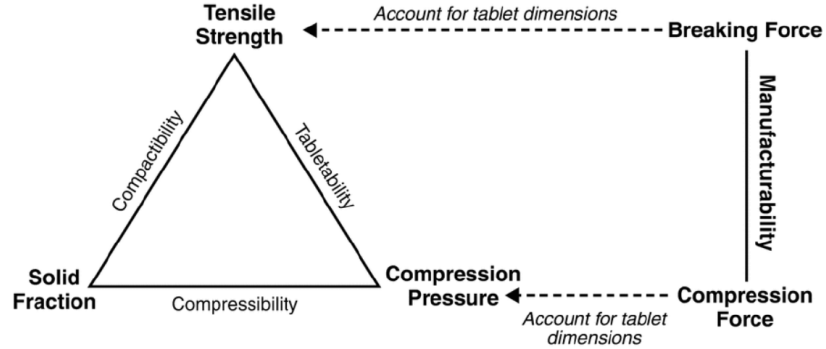


USP/NF ⟨1062⟩ TABLET COMPRESSION CHARACTERIZATION (25.08.2020)

Compressibility profile

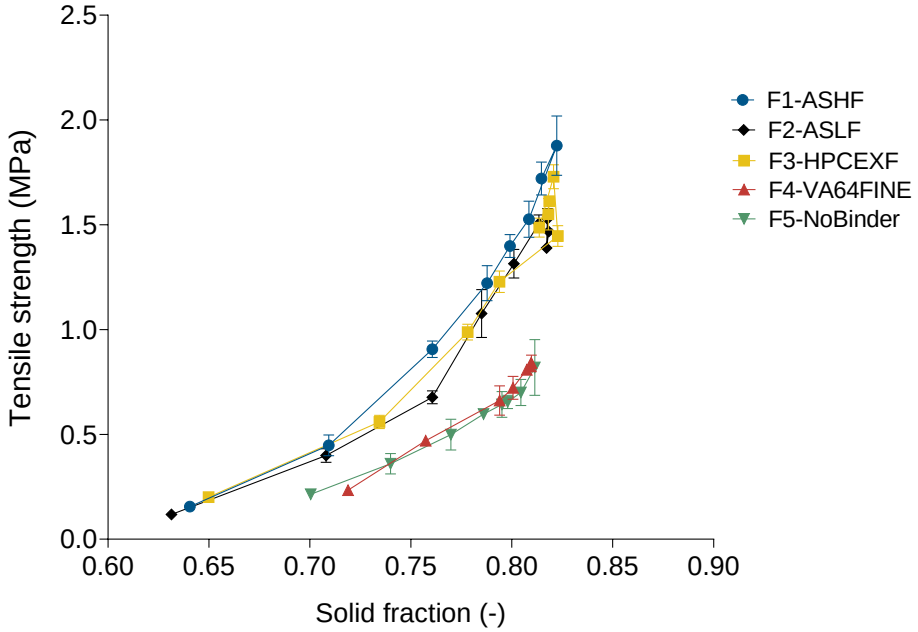


Compaction analysis



USP/NF ⟨1062⟩ TABLET COMPRESSION CHARACTERIZATION (25.08.2020)

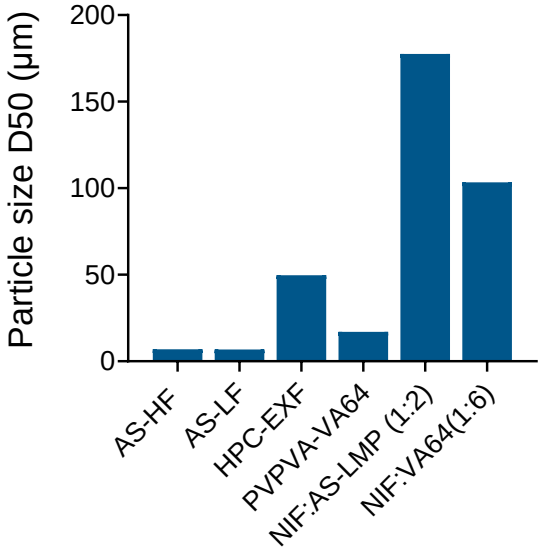
Compactibility profile



Results:

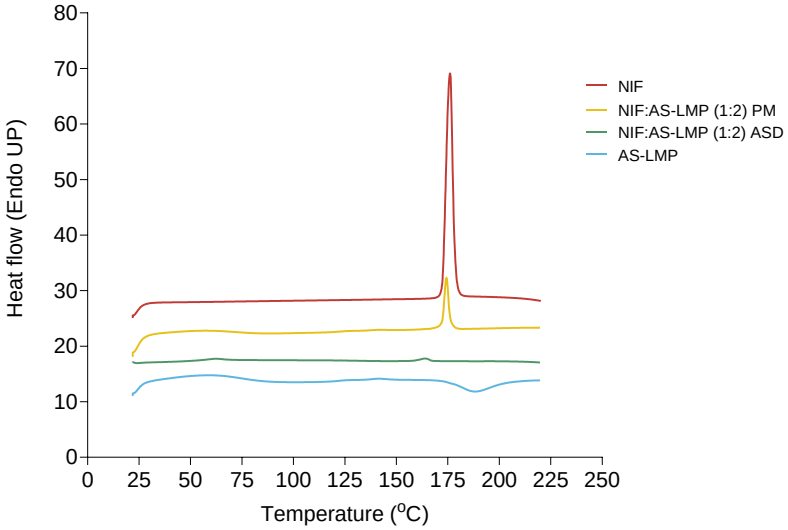
Particle size

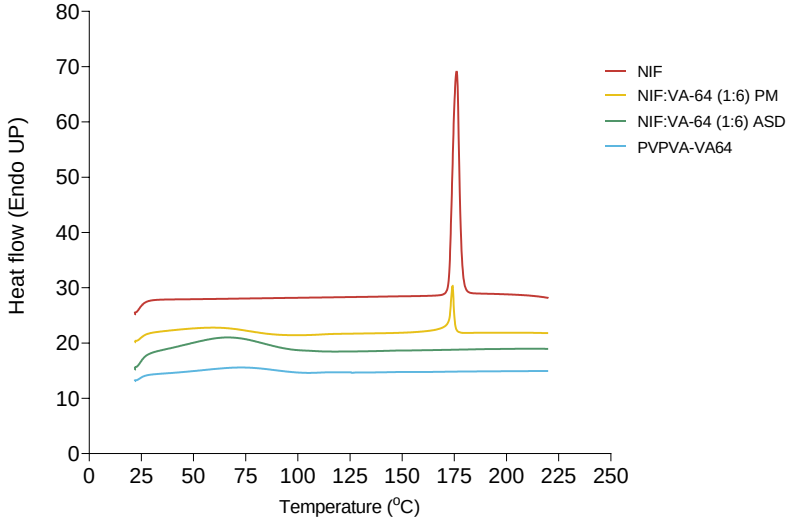
	AS-HF	AS-LF	HPC-EXF	PVPVA-64	NIF/AS-LMP (1:2)	NIF/PVPVA-64 (1:6)
D50 (µm)	6.93	6.83	49.71	16.96	177.51	103.38



Results:

Differential scanning calorimetry





Summary and conclusions

- After reaching supersaturation state, **API precipitation and re-crystallization** is common with ASD formulations using different carrier polymers
- **Adding precipitation inhibitors (PI)** can solve this problem and prolong supersaturation state.
- We demonstrated the **double action of HPMCAS (Shin-Etsu AQOAT® AS-HF) as a tablet binder and PI in ASD formulations prepared by hot-melt extrusion**.
- Independent of ASD polymeric carrier (AS-LMP or VA64), **adding HPMCAS AS-HF improved the supersaturation and precipitation inhibition**.
- Applied in a tablet formulation, **utilizing AS-HF as dry binder showed an improved tablet tensile strength better tabletability profile** vs. typical used dry binder as HPC-EXF and also Kollidon VA64 fine.