Improving the Drug Loading Capacity and Downstream Processing of HPMCAS using Gelucire® 48/16 in Hot-Melt Extrusion

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PURPOSE

- Improving the drug loading capacity and downstream processability of Hydroxypropyl Methylcellulose Acetate Succinate (HPMCAS, Shin-Etsu AQOAT®) in hot-melt extrusion-based amorphous solid dispersions (ASDs) is necessary to reduce the pill burden and optimize drug release and tablet properties (1–3).
- In this work, we evaluated the co-processing of a lipid surfactant, Gelucire® 48/16, polyoxyl-32 stearate (G4816) with HPMCAS (ASMMP) in ASD formulations of nifedipine (NIF) and fenofibrate (FF).

METHODS

- Gelucire® 4816 was frozen overnight (- 20 ºC) then micronized using a mortar and pestle into fine powder and sieved with a mesh #60 (250 µm).
- NIF or FF were blended with HPMCAS and Gelucire® 48/16 for 10 minutes using Turbula mixer according to **Table 1**.
- HME was conducted using a PHARMA 11 twin-screw extruder (Thermo Fisher, Germany) and the process parameters are presented in **Table 2.**
- Extruded filaments were milled using a hammer-mill (Frewitt, Germany) at 15,000 rpm through a 1 mm sieve and evaluated for particle size distribution (PSD) using a Sympatec® laser diffraction particle size analyzer.
- Milled extrudates were re-milled through a 0.5 mm sieve and compacted into tablets according to the formulation described in **Table 3 and 4.**
- Tablet properties (hardness and disintegration time) were evaluated using an Erweka® hardness and disintegration tester.
- *In vitro* drug release testing for NIF tablet formulations was carried out using a USP-II dissolution apparatus (n = 3) in 1000 mL of PBS (pH = 6.8), 75 rpm, 37ºC and drug concentration was evaluated using an established HPLC-UV method.
- *In vitro* drug release testing for FF tablet formulations was carried out using the same apparatus (n = 3) in 500mL of PBS (pH = 6.8) with 0.025M sodium lauryl sulfate (SLS), 75 rpm, 37 ºC and drug concentration was evaluated using an established HPLC-UV method.

Table 1: HME formulations

Ingredients	F1	F2	F3
	(%)	(%)	(%)
NIF	33	20	-
FF	-	-	20
AS-MMP	57	70	60
Gelucire® 48/16	10	10	20
Total	100	100	100

Table 2: HME process parameters

	NIF formulations	FF formulation
Screw design	Standard HME with 2 kneading zones	
Screw speed (rpm)	150	50
Feed rate (g/min)	6	5
Die size (mm)	2	2
Temperature (ºC)	**Zone 1:** 90, **Zone 2 – 8**: 175	**Zone 1:** 60, **Zone 2 – 8**: 160

Table 3: Tablet formulations

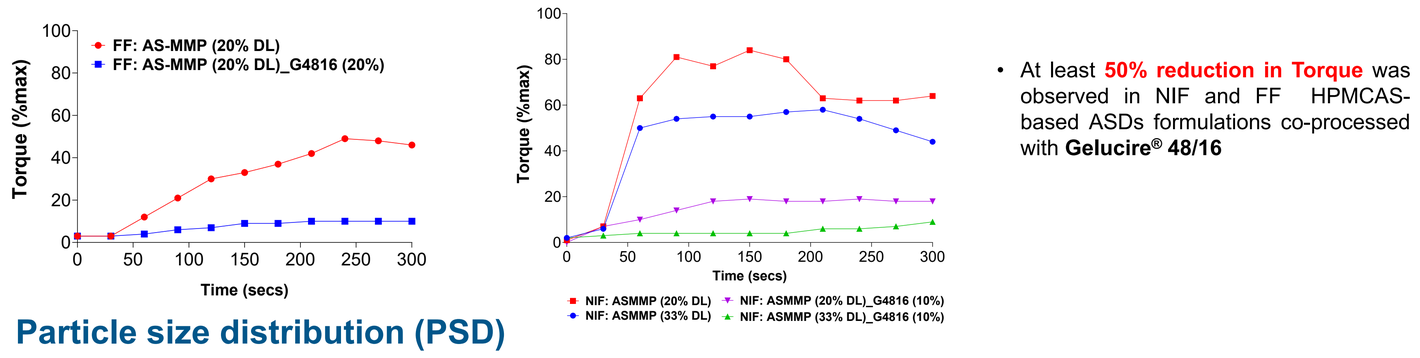
Ingredient	Function	(%)
ASD	Enhance solubility	50
MCC (PH-102)	Filler	43
L-HPC (LH-21)	Binder - Disintegrant	5
Compritol 888 ATO	Lubricant	2

Table 4: Tablet properties

Property	Value
Weight (mg)	400
Compaction (kN)	5, 15, 25
Dimensions	10.mm curved face

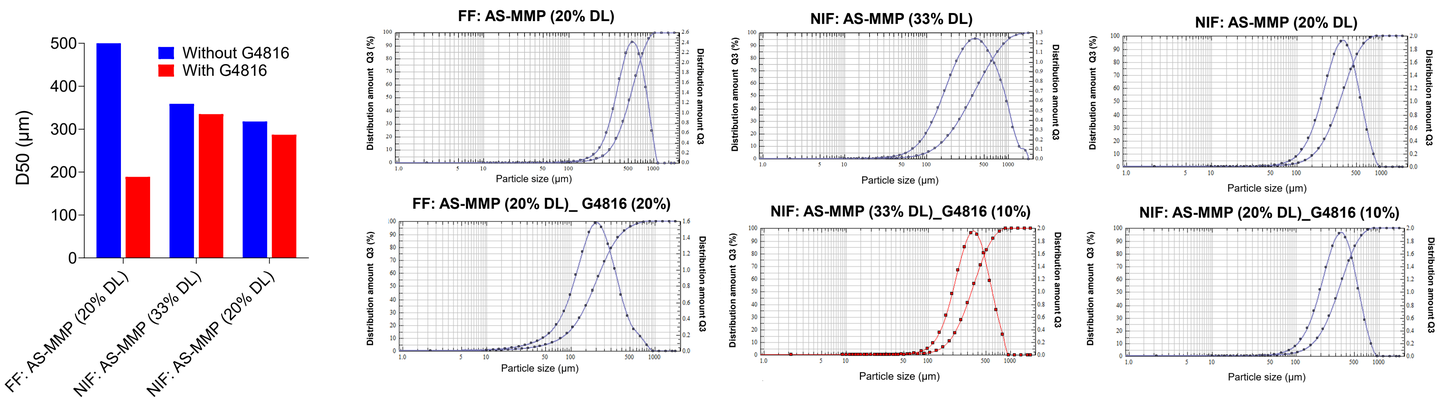
RESULTS

• HME Torque



- At least **50% reduction in Torque** was observed in NIF and FF HPMCAS-based ASDs formulations co-processed with **Gelucire® 48/16**

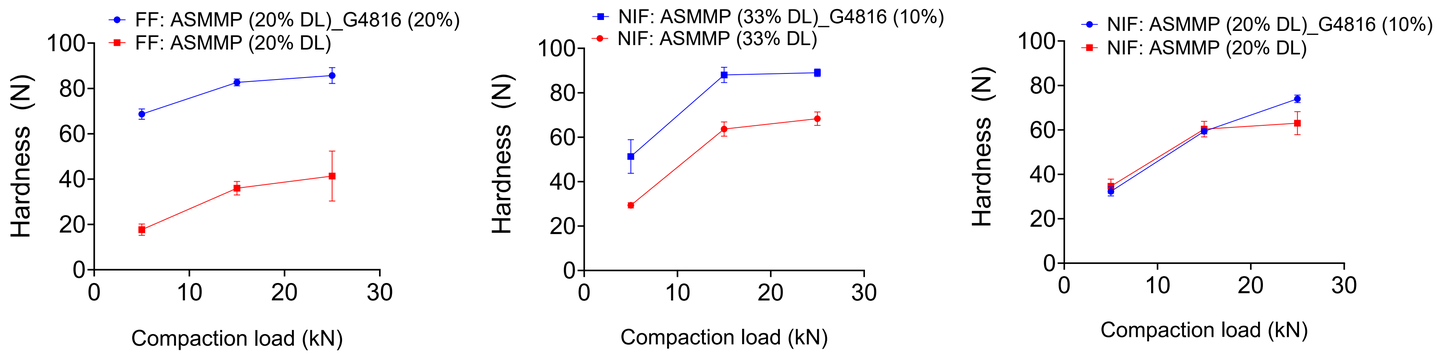
• Particle size distribution (PSD)



→ Co-processing Gelucire® 48/16 (20%) with FF: AS-MMP (20% DL), resulted in a 2.7-fold reduction in particle size D50.

→ Co-processing Gelucire® 48/16 (10%) with NIF: AS-MMP (33% DL) or (20% DL), resulted in a minimal reduction in particle size D50.

• Tablet Hardness

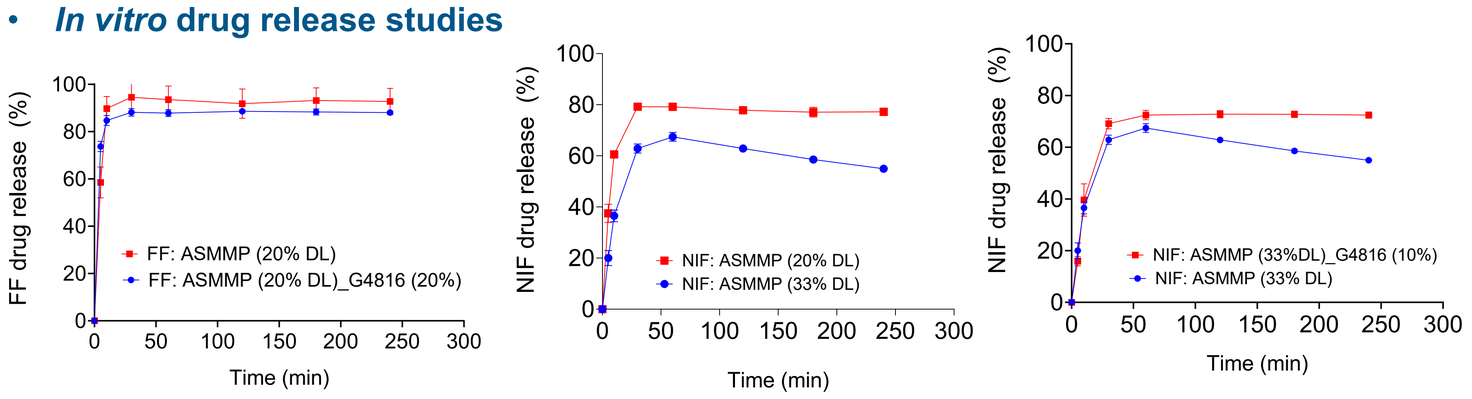


→ Co-processing G4816 (20%) with FF: AS-MMP (20% DL) resulted in a 2.3-fold increase in average tablet hardness.

→ Co-processing G4816 (10%) with NIF: AS-MMP (33% DL) resulted in 1.4-fold increase in average tablet hardness.

→ Co-processing G4816 (10%) with NIF: AS-MMP (20% DL) avoided over compaction at higher compaction loads.

• *In vitro* drug release studies



→ Co-processing G4816 (20%) with FF: AS-MMP (20% DL) resulted in no significant difference in drug release.

→ Without G4816, high drug load of NIF (33%) in the NIF: AS-MMP (1:2) formula, results in drug crystallization after 1 hour, while the lower drug load formulation (20%) results in complete release of NIF (80%).

→ Adding G4816 (10%) to the high drug load formulation, NIF: AS-MMP (1:2), prevents the drug crystallization and results in complete (80%) drug release.

CONCLUSION

- Co-processing of Gelucire® 48/16 in HPMCAS-based ASDs of NIF and FF improved the downstream processability as reflected in torque, particle size D50 reduction, and improved tablet hardness.
- Further, this approach improved the drug loading capacity, enhancing the drug release and maintaining its supersaturation in high drug load ASD formulation of NIF (33% DL).
- The study highlights the utility of combining lipid surfactants with HPMCAS-based ASDs in hot melt extrusion (HME) to improve the downstream processing and drug release, ultimately reducing the pill burden and improving patient's compliance with the treatment.

REFERENCES

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