HPMC Acetate Succinate: An ideal polymer for solubility enhancement

Improving aqueous solubility of API has always been a challenge. There are many techniques devised over a period of time for improving solubility of API namely, size reduction, salt formation, micellar solubilization, co-solvency, crystal modification, complexation, lipid based carrier systems, and amorphous solid dispersions. All these techniques have been commercially utilized with variable success, depending on the solubilization potential, stability of the system, and production cost. One such method that has enjoyed commercial success is formulation of solid dispersion.

Solid dispersion is defined as a dispersion of one or more active moiety in a suitable inert carrier or matrix in a solid state. This technique has been one of the choice of improving solubility of API and has undergone many modifications/enhancements to improve its utility. Amorphous solid dispersion is one such method. Amorphous solid dispersions are molecular mixtures of poor water soluble API with hydrophilic carriers, responsible for modulating release profile of API, and characterized by the reduction of particle size to a molecular level solubilizing or co-dissolving the API in the soluble carriers. As the name suggests these are amorphous systems with high thermodynamic energy entrapped in polymer network that prevent recrystallization of API.

The two major critical parameters in developing ASDs are formulation method and polymer selection. ASDs can be manufactured by solvent methods and melting methods. The widely used methods include spray drying, spray granulation or hot melt extrusion technique. The choice of manufacturing method depends to a large extent on API properties.

There are by far only a handful of polymers utilized in the formulation of ASDs, of which about 50% of the marketed formulations contain Hypromellose Acetate succinate (HPMCAS). Shin-Etsu, a Japanese company has been a pioneer in the development of HPMCAS. The polymer, branded as AQOAT®, received approval in 1987 as a polymer having pH depend solubility, utilized primarily as a polymer for enteric coating. HPMCAS is an amphiphilic derivative of Hypromellose, with is acetate and methyl groups acting as hydrophobic domains and succinoyl groups as hydrophilic ones. Due to its amphiphilic nature, HPMCAS was found to be helpful as a carrier for ASDs.

Shin-Etsu AQOAT® is available in 9 grades, as mentioned in Table 1. The polymer is robust and is amenable to be processed by any of the manufacturing methods mentioned earlier. The MP grades have been specifically designed for use in hot melt extrusion (HME) process.

Grades	**Fine Grade**	**AS-LF**	**AS-MF**	**AS-HF**
	Medium Particle size	**AS-LMP**	**AS-MMP**	**AS-HMP**
	Granular Grade	**AS-LG**	**AS-MG**	**AS-HG**
Acetyl Content		5.0-9.0%	7.0-10.0%	10.0-14.0%
Succinoyl Content		14.0-18.0%	10.0-14.0%	4.0-8.0%
pH Solubility		5.5 and above	6.0 and above	6.5 and above
Average Particle size	F-grade	Not more than 10µm		
	MP-grade	70-300µm		
	G-grade	Around 1000µm		

AQOAT® has been found to be an ideal polymer for HME process. The polymer is thermoplastic in nature with glass transition temperature around 115-125 °C and degradation temperature of 200 °C. The wide processing window ensures flexibility for its use in HME process. Also, it exhibits low melt viscosity compared to any other polymer at its processing temperature, a property that is again beneficial for HME processing.

The amphiphilic nature of AQOAT® helps to inhibit recrystallization of API during the shelf life of the formulation. The hydroxypropoxy molar substitution influences Tg of the polymer and the acetyl: succinoyl ratio influences the degree of supersaturation. By careful selection of polymer grade, a stable formulation can be formulated for a variety of APIs exhibiting poor solubility. Hence, there are many formulations available in global market utilize HPMCAS as a carrier for ASDs. The following list summarize these formulations.

- Orkambi (Lumacafactor & Ivacaftor)
- Ferriprox (Deferiprone)
- Pifeltro (Doravirine)
- Noxafil (Posaconazole)
- Erleada (apalutamide)
- Idhifa (Enasidenib mesylate)
- Qinlock (Ripretinib)
- Delstrigo (Doravarine, Lamuvidine & Tenofovir)
- Zelboraf (Vemurafenib)
- Kalydeco (Ivacaftor)
- Symdeko (Tezacaftor & Ivacaftor)
- Trikafta (Elexacaftor, tezacaftor & ivacaftor)
- Welireg (Belzutifan)

For more information on Ceolus please visit our manufacturer's page.

For sample request you can contact our representative here.