Overview of extensively employed polymeric carriers in Solid Dispersion Technology.

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S. no	Polymer Grade	Viscosity mPas	Density (g/mol) ^a	Heat Capacity (J/gm.K)ª		
1	PVP K-12	1.3 – 2.3	1.04	0.37		
2	PVP K-15	1.5 – 3.5				
3	PVP K-30	5.5 – 8.5	1.12	0.28		
4	PVP K-60	-				
5	PVP K-90	300-700	1.21	0.29		
6	PVP K-120	-				
Reference						

Table I: Various grades of PVP and relevant properties thereof.

a Knopp M et al., (2015) [69].

Table II: Various grades of pharmaceutically relevant HPMC and relevant properties thereof.

SN	HPMC Grade ^a	% Methoxy	% Hydroxypropoxy	% Moisture (%) ^ь	
1	HPMC E	28 - 30	7 – 12	3.92	
	(USP 2910)	(29)	(8.5)		
2	HPMC F	27 - 30	4 - 7.5	3.98	
	(USP 2906)	(28)	(5.0)		
3	НРМС К	19 – 24	7 – 12	4 7 2	
	(USP 2208)	(22)	(8.1)	4.73	

^a Subtype of respective polymer is 4M representing molecular weight 4000 g/mol [126].

^b Moisture content measured by employing TGA analysis [43].

Values in the parentheses represent the USP limits.

HPMCAS Grade Properties	L Grade	M Grade	H Grade
Acetyl Content	5 - 9%	7 - 11%	10 - 14%
Succinoyl Content	14 - 18%	10 - 14%	4 - 8%
Methoxyl Content	20 - 24%	21 - 25%	22 - 26%
Hydroxypropoxy Content	5 – 9%	5 – 9%	6 - 10%

Table III: Different grades of HPMCAS and its properties

L, M, H grade: Different grades of HPMCAS; each grade is available in 2 different particle size: fine (F) and granular (G).

Reference: AquaSolve[™] hypromellose acetate succinate (hydroxypropyl methylcellulose acetate succinate or HPMCAS). https://www.ashland.com/industries/pharmaceutical/oral-solid-dose/aquasolve-hypromellose-acetate-succinate (accessed Jun 14, 2020).

SN.	Trade Name	API	Polymer excipient	Dosage form	Preparation techniques		Manufactured by	
PEG								
1	Gris-PEG®	Griseofulvin	PEG	Tablet	Melt method	1975	Pedinol Pharmacal Inc.	
PVF	PVP							
1	Cesamet®	Nabilone	PVP	Tablet	Solvent evaporation	1985	Valeant	
2	Kaletra®	Ritonavir/ Lopinavir	PVP-VA64	Tablet	HME	2007	Abbott	
3	Norvir®	Ritonavir	PVP-VA64	Tablet	HME	2010	Abbott	
HPN	4C							
1	Isoptin® ER-E	Verapamil	HPC/HPMC	Tablet	HME	1982	Abbott	
2	Nivadil®	Nivaldipine	HPMC	Tablet	HME	1989	Fujisawa	
3	Sporanox®	Itraconazole	НРМС	Capsule	Fluid-bed bead layering	1992	Janssen	
4	Prograf®	Tacrolimus	НРМС	Capsule	Spray drying	1994	Astellas Pharma Inc.	
5	Rezulin®#	Troglitazone	PVP/HPMC	Tablet	N/A	1997	Pfizer	
6	Crestor®	Rosuvastatin	HPMC	Tablet	Spray drying	2002	Astra Zeneca	
7	Zithromax®	Azithromycin	HPMC	Tablet	HME	2002	Pfizer, Inc	
8	Eucreas®	Vildagliptin + Metformin Hydrochloride	НРМС	Tablet	HME	2007	Novartis	
9	Intelence®	Etravirine	НРМС	Tablet	Spray drying	2008	Janssen	
10	Modigraf®	Tacrolimus	НРМС	Granules for oral suspension	Spray drying	2009	Astellas Pharma Europe B.V.	
11	Samsca®	Tolvaptan	НРМС	Tablet	Granulation	2009	Otsuka Pharma	
12	Zortress®	Everolimus	НРМС	Tablet	Spray drying	2010	Novartis Pharmaceuticals	
13	Onmel®	Itraconazole	HPMC	Tablet	HME	2010	Stiefel	
14	Certican®	Everolimus	HPMC	Tablet	HME	2012	Novartis	
15	Incivo®	Etravirine	HPMC	Tablet	N/A	2012	Janssen	
16	Astragraf XL®	Tacrolimus	НРМС	Capsule	Wet granulation	2013	Astellas Pharma Inc.	
17	Isoptin-SRE®	Verapamil	HPC/HPMC	Tablet	HME	2015	AbbVie Inc.	
18	Envarsus® LCPTacrolimus	Tacrolimus	Poloxamer/ HPMC	Tablet	Melt dose technology	2015	Veloxis Pharmaceuticals	
19	Zepatier®	Elbasvir/ Grazoprevir	TPGS, Copovidone, and HPMC	Tablet	Spray drying	2016	Merck	
20	LCP-Tacro®	Tacrolimus	НРМС	Tablet	N/A	N/A	LifeCycle Pharma	
HP	HPMCAS							
1	Cymbalta®	Duloxetine	HPMCAS	Capsule	N/A	2004	Eli Lilly	

Table IV: List of marketed solid dispersion product containing PEG, PVP, HPMC and HPMCAS

SN	Trade Name	API	Polymer	Dosage	Preparation	Year of	Manufactured
514.	Haue Maine		excipient	form	techniques	launch	by
2	Incivek®	Telaprevir	HPMCAS	Tablet	Spray drying	2011	Vertex
			III MCAS				Pharmaceuticals
					Solvent		
3	Zelboraf®	Vemurafenib	HPMCAS	Tablet	controlled	2011	Roche
_					precipitation		
4	Kalydeco®	Ivacaftor	HPMCAS	Tablet	Spray drying	2012	Vertex
							Pharmaceuticals
5	Nofaxil®	l® Posconazole	HPMCAS/	Tablet	HME	2013	Merck
5			HPC				Merck
6	Orkambi®	Lumacaftor/	HPMCAS/	Tablet	Spray drying	2015	Vertex
		Ivacaftor	SLS				Pharmaceuticals
7	Torcetrapib®#	Torcetrapib	HPMCAS	Tablet	N/A	N/A	Pfizer

#product withdrawn from market.

HME: Hot Melt Extrusion

N/A: Not available

Reference: [88, 41], and Vasconcelos, T., Marques, S., Neves, J. D., & Sarmento, B. (2016). Amorphous solid dispersions: Rational selection of a manufacturing process. Advanced Drug Delivery Reviews, 100, 85-

101.

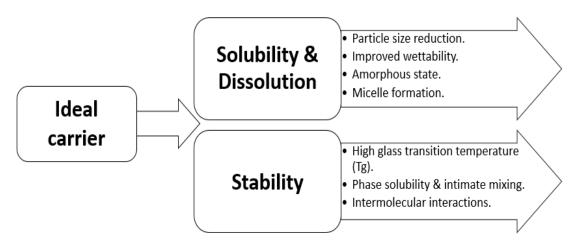


Figure 1: Characteristics of ideal carrier.

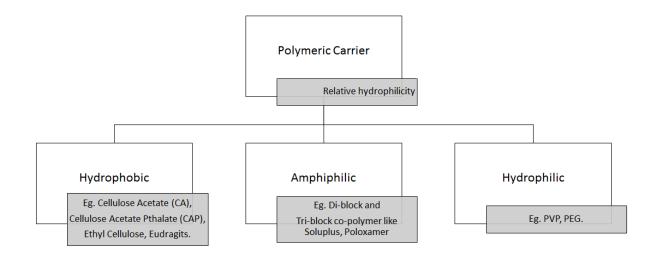


Figure 2: Classification of polymeric carriers based on relative hydrophilicity.

PVP – Polyvinyl Pyrrolidone

PEG – Polyethylene Glycol

HPMC – Hydroxy Propyl Methyl Cellulose

HPMCAS - Hydroxy Propyl Methyl Cellulose acetate succinate

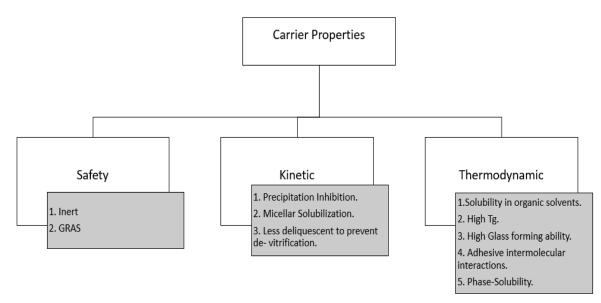


Figure 3: Classification based on carrier properties.

GRAS – Generally Regarded As Safe

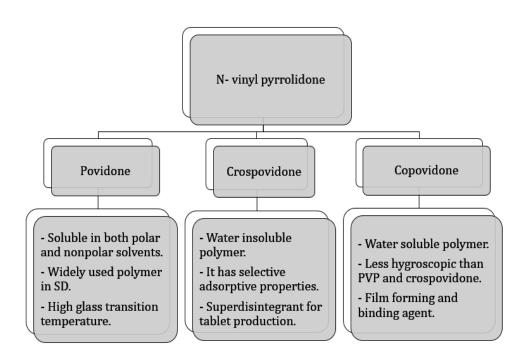


Figure 4: Classification of N- vinyl pyrrolidone based on crosslinking.

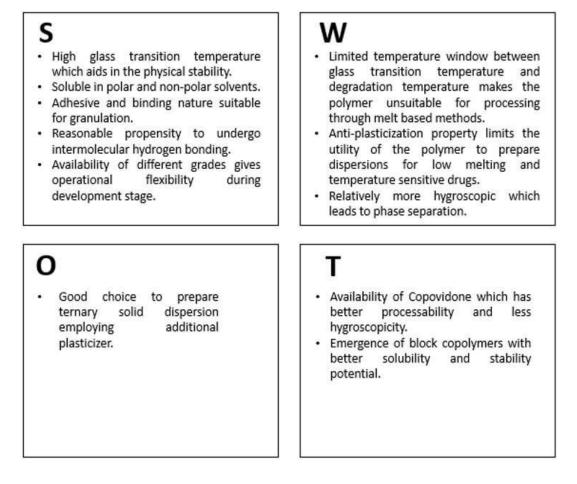


Figure 5: SWOT analysis of PVP with regard to its implementation in solid dispersions.

SWOT – strengths, weaknesses, opportunities, and threats

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dissolution

polymer.

- Less hygroscopic than PVP.
- Wider temperature window between glass transition and degradation temperature which can be utilized for melt base methods.
- Available in consistent particle size of 100μm.
- Phase solubility with wide range of APIs

Can be formulated into ternary solid

dispersion along with surfactant to

prevent API recrystallisation during

Can be employed to generate

nanoparticles post rapid dissolution

of amorphous domains of the

W

- Relatively more hygroscopic when compared to Soluplus and PEG
- Leads to *insitu* recrystallisation during dissolution of low Tg drugs.

Т

- Relatively less hygroscopic polymers like Soluplus[®] and PEG has a potential to provide efficacious alternative.
- The presence of other amphiphilic polymers which have a potential to form colloidal phase of nano dimension.

Figure 6: SWOT analysis of Copovidone with regard to its implementation in solid dispersions.

API – Active Pharmaceutical Ingredient

- High solubility in aqueous and organic solvents.
- Ability to form nano and micro range dispersions in solid state.
- Good wettability which translates into dissolution improvement.
- Low toxicity.

W

- Crystalline polymer.
- Poor drug-polymer miscibility and thus demonstrated to form monotectics than eutectics.
- Polymer recrystallization after long term storage.
- Glass forming ability of APIs dictate the physical stability of the dispersion and not the polymer itself.

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- Can be employed in ternary dispersions due to the dissolution advantage.
- Holds potential to improve permeability due to its ability to generate nano and micro dimension particles.
- Can be employed to formulate solid dispersions of low melting drugs through HME.

Т

- Availability of amorphous and strong glass forming polymers.
- Can be easily replaced by polymers like HPMC and Soluplus which have API independent physical stability unlike PEG.

Figure 7: SWOT analysis of PEG with regard to its implementation in solid dispersions.

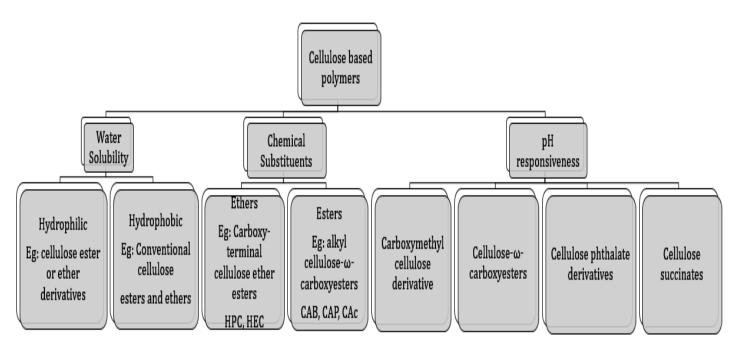


Figure 8: Classification of cellulose based polymer based on water solubility, chemical substituents and pH responsive behaviour. [Part of the classification is reproduced from reference 41]

HPC: Hydroxypropyl cellulose

HEC: Hydroxyethyl cellulose

CAc: Cellulose acetate

CAP: Cellulose acetate-propionate

CAB: Cellulose acetate-butyrate

- High glass transition temperature which aids in the physical stability.
- Hydrophilic polymer aids in the dissolution.
- Recrystallization inhibition potential.
- Resistant to hydrolysis and unabsorbed from GIT.
- Excellent biocompatibility and low toxicity.

W

- Poor drug-polymer miscibility for certain lipophilic APIs.
- Unlike HPMCAS, not pH responsive.
- Lacks the ability to form strong intermolecular interactions.
- Limited temperature window between glass transition and degradation temperature of the polymer may limit the utility in melt based preparation methods.

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- Can be used to formulate ternary dispersions of low melting APIs by using plasticizer.
- Can be implemented to form in-situ nanoparticles post dissolution.
- Can be used to generate sustained supersaturation by the virtue of crystallization inhibition properties of the polymer.

Т

- The emergence of polymers like Soluplus which are efficient in dissolution and stability improvement.
- Availability of HPMCAS which is relatively less hygroscopic and pH responsive derivative of cellulose.

Figure 9: SWOT analysis of HPMC with regard to its implementation in solid dispersions.

GIT – Gastrointestinal Tract

- Reasonably high glass transition temperature which aids in the physical stability.
- High propensity to form intermolecular hydrogen bonding.
- Strong precipitation /or recrystallization inhibition potential.
- pH dependent solubility and ionization due to presence of succinic acid moiety.
- Availability of different grades gives operational flexibility during development stage.

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- Can be used to generate sustained supersaturation and colloidal phase during dissolution.
- Can be leveraged to formulate pH responsive drug delivery systems.

W

- Limited solubility below pH 4, which may hamper the immediate release of the solid dispersion.
- The method of the polymer synthesis is complicated and inconsistent, which warrants rigorous raw material analysis to prevent batch to batch variability.

Т

- The emergence of polymers like Soluplus which are efficient in dissolution and stability improvement.
- The polymer can be replaced in the future by polymers exhibiting low moisture uptake and high thermal stability.

Figure 10: SWOT analysis of HPMCAS with regard to its implementation in solid dispersions.

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- Amphiphilic in nature.
- Generation of colloidal phase of nano dimension during dissolution.
- Less hygroscopic.
- Phase solubility with wider range of APIs.
- Large temperature window of almost 170 °C available between glass transition and degradation temperature which enables the processing through melt methods, in particular HME.

W

- Swelling properties may hinder drug release for low drug load dispersions.
- Formation of mixed micelles in biorelevant media may offset the dissolution advantage.

Т

- May be replaced by a futuristic polymer due to generation of mixed micelles during biorelevant dissolution which leads to inconsistent dissolution.
- dispersion of dissimilar melting APIs (Pair of high and low melting APIs) through melt methods.
 polymer swelling properties can be

· Suitable to prepare multicomponent

leveraged to prepare delayed release drug delivery

Figure 11: SWOT analysis of Soluplus® with regard to its implementation in solid dispersions.

Fikentscher's k-value:

The K-values assigned to various grades of PVP polymer represents a function of the average molecular weight, the degree of polymerization, and the intrinsic viscosity. The K-values are derived from viscosity measurements and are calculated according to Fikentscher's formula. As a measure of the mean molecular weight of a polymeric substance, Fikentscher derived the k value from measurements of the relative viscosity of solutions of polymer solutions. The k value is calculated by applying the following equation:

$$\frac{\eta_c}{\eta_0} = \left(\frac{75 * k^2}{1 + 1.5 * k * c} + k\right) * c$$

Where:

c = concentration in g/100 ml. η_c = viscosity of the solution. η_0 = viscosity of the solvent. k = value according to Fikentscher (K = 1000* k)