A Quality by Design Approach to Optimize Tablet Formulations containing PVP VA64 Amorphous Dispersions: Formulation Variables

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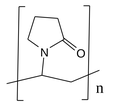
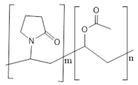
PURPOSE

- Amorphous solid dispersions (ASDs) manufactured using techniques such as hot-melt extrusion, co-precipitation and spray drying help enhance API bioavailability
- Polymers such as Polyvinyl pyrrolidone co-vinyl acetate 64 (PVP VA64) and Polyvinylpyrrolidone (PVP K30) often lead in screening experiments due to stability enhancement, solubilization and crystallization inhibition capabilities
- However, hydrophilic polymers as such have strong binding and gelation properties, which frequently presents a disintegration/dissolution performance challenge for dosage forms



Kollidon K30 (Povidone)
Polyvinylpyrrolidone



Kollidon VA-64 (Copovidone)
vinylpyrrolidone-vinyl acetate copolymer

Water-soluble polymers such as **HPMC, Soluplus and copovidone** reportedly depict gelling phenomenon

Tablets demonstrate a viscous layer on the outside with defined boundaries (gel block) and a dry tablet core

Water penetration to the tablet core blocked, hindering formation of primary particles

Long Disintegration Times

OBJECTIVE(S)

The goal of this work is to utilize a Quality by Design (QbD) approach to generate a design space for tablet formulations of PVP VA64 ASDs

1. Evaluate different formulation variables to identify main effects and their impact on the tablet critical quality attributes (CQA) (dependent variables/responses)
2. Evaluate tableting additives such as inorganic salts and dietary sugars and impact on tablet CQA

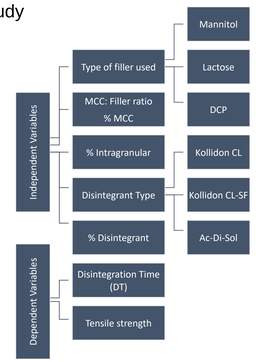
METHOD(S)

- 8-run screening design (Fig 1) was generated with a D-optimality criterion
  - Different type of filler and disintegrant (Categorical variables, Fig 2)
  - MCC: Filler ratio (% MCC, 33 – 67%) and Disintegrant (5-15%) loading (Continuous variables)
  - MCC was utilized across all formulations as the ductile filler in a ratio with the brittle fillers as we tried to optimize this ratio
  - % Intragranular addition was maintained around 90% (monitored, not included in the initial screen)
- Design was augmented with 6 additional runs to study certain effects in further detail
  - Limits on % Disintegrant were narrowed (8-10%)
  - Limits on % MCC were expanded (20-80 %)
  - Limits on % Intragranular addition were expanded (60-90%)
- This data was fit using Standard Least Squares.

Fig 1. 8-run Screening Design at different levels of independent variables

Design				
Run	Disintegrant Type	Disintegrant Conc.%	Filler Type	MCC:Filler Ratio (MCC wt%)
1	Kollidon CL	5	Lactose	33.33
2	Ac-Di-Sol	5	Mannitol	66.67
3	Kollidon CL-SF	5	DCP	66.67
4	Ac-Di-Sol	15	DCP	33.33
5	Kollidon CL	15	DCP	66.67
6	Ac-Di-Sol	15	Lactose	66.67
7	Kollidon CL-SF	15	Mannitol	33.33
8	Kollidon CL	10	Mannitol	50

Fig 2. Independent and dependent variables as a part of the screening study



METHOD(S)

- Master formulae for all the 16 formulations are listed in Table 1.
- The formulations were manufactured by a bench-scale dry granulation process as depicted in Fig 3

Fig 3. Process train used for manufacture of tablets

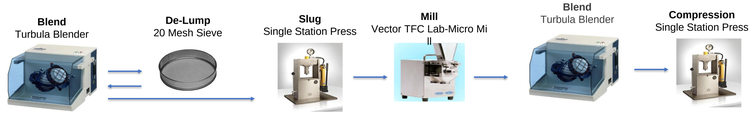


Table 1. Master Formulae for 14 formulations from the DOE and 2 additional runs with formulation additives

	Prototype Formulations															
	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12	F13	F14	F15	F16
Component	Unit Composition (by weight %)															
40:60 Z160:PVP-VA64 ASD	35.00%	35.00%	35.00%	35.00%	35.00%	35.00%	35.00%	35.00%	35.00%	35.00%	35.00%	35.00%	35.00%	35.00%	35.00%	35.00%
Microcrystalline Cellulose (Avicel PH-105)	14.14%	33.67%	11.00%	27.00%	27.00%	33.67%	21.50%	11.00%	9.75%	18.50%	3.90%	15.60%	12.66%	9.62%	9.62%	12.66%
Lactose Monohydrate (FloLac 90)	38.86%	-	-	16.00%	16.00%	-	-	-	-	-	-	-	-	-	-	-
Emcompress (DCP)	-	19.33%	32.00%	-	-	-	-	-	-	-	-	-	-	-	-	-
Parteck M100 (Mannitol)	-	-	-	-	-	19.33%	26.50%	32.00%	9.75%	18.50%	15.60%	3.90%	35.34%	28.38%	28.38%	25.34%
Kollidon CL-SF (Crospovidone)	-	2.50%	-	-	-	-	-	7.50%	-	-	-	-	-	-	-	-
Kollidon CL (Crospovidone)	2.50%	-	-	7.50%	-	-	5.00%	-	4.00%	4.00%	4.00%	4.00%	-	-	-	-
Croscarmellose Sodium (Ac-Di-Sol)	-	-	7.50%	-	7.50%	2.50%	-	-	-	-	-	-	5.00%	5.00%	5.00%	5.00%
Sodium Chloride (Powder Grade)	-	-	-	-	-	-	-	-	-	-	-	-	-	5.00%	-	-
Sucrose (Di-Pac Tableting Sugar)	-	-	-	-	-	-	-	-	-	-	-	-	-	-	5.00%	-
Colloidal Silicon Dioxide	1.00%	1.00%	1.00%	1.00%	1.00%	1.00%	1.00%	1.00%	1.00%	1.00%	1.00%	1.00%	1.00%	1.00%	1.00%	1.00%
PRUV SSF	0.50%	0.50%	0.50%	0.50%	0.50%	0.50%	0.50%	0.50%	0.50%	0.50%	0.50%	0.50%	0.50%	0.50%	0.50%	0.50%
Intragranular Total	92.00%	92.00%	87.00%	87.00%	87.00%	92.00%	89.50%	87.00%	60.00%	77.50%	60.00%	60.00%	89.50%	84.50%	84.50%	79.50%
Microcrystalline Cellulose (Avicel PH-200)	5.00%	5.00%	5.00%	5.00%	5.00%	5.00%	5.00%	5.00%	17.75%	9.00%	7.10%	28.40%	5.00%	5.00%	5.00%	5.00%
Parteck M200 (Mannitol)									17.75%	9.00%	28.40%	7.10%				10.00%
Kollidon CL-SF (Crospovidone)		2.50%						7.50%								
Kollidon CL (Crospovidone)	2.50%			7.50%	7.50%		5.00%		4.00%	4.00%	4.00%	4.00%				
Croscarmellose Sodium (Ac-Di-Sol)			7.50%			2.50%							5.00%	5.00%	5.00%	5.00%
Sodium Chloride														5.00%		
Sucrose															5.00%	
PRUV SSF	0.50%	0.50%	0.50%	0.50%	0.50%	0.50%	0.50%	0.50%	0.50%	0.50%	0.50%	0.50%	0.50%	0.50%	0.50%	0.50%
Extragranular Total	8.00%	8.00%	13.00%	13.00%	13.00%	8.00%	10.50%	13.00%	40.00%	22.50%	40.00%	40.00%	10.50%	15.50%	15.50%	20.50%
Total	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%

RESULTS

DESIGN OF EXPERIMENTS

- As depicted in Table 2., Disintegrant Type, % Disintegrant, and Filler Type had a statistically significant impact on the DT (min) whereas % MCC loading had a statistically significant impact on Tensile Strength (MPa)
- Fig 4 depicts the effects of different responses:
- Ac-Di-Sol demonstrated quickest DT with good tensile strength, making it most desirable
- With the use of Kollidon CL-SF, we observe steady increase in DT
- We observe speeding of DT with increase in % Disintegrant, however we see that this effect plateaus at ~9% from the Desirability graph
- Mannitol is the most desirable Filler; this can be attributed to quicker DT and comparable Tensile strength.
- % Intragranular does not impact DT, however a slight trend is observed with loss in tablet tensile strength as we add more material intragranularly
- % MCC loading does not impact DT, however, a greater MCC: Filler ratio increases the tensile strength of the formulation

NON-SINK DISSOLUTION

- F4 & F5 demonstrated 1.2 times increase in AUC over the neat ASD (Fig 5) – high level of disintegrating agent (15%) regardless of the disintegrating agent type
- F14 demonstrates 1.4 times increase in AUC over the neat ASD - presence of NaCl speeds DT. The rationale behind this can be seen in Fig 6, wherein researchers demonstrate quicker penetration of water in hydrophilic matrices in the presence of NaCl
- F7, F13 and F15 have 10% disintegrant, slowing DT (>210 min) and in turn the drug released
- Disintegrant type, MCC: Filler Ratio did not impact the slow release
- Presence of dietary sugar additive, Sucrose, did not help this formulation

CONCLUSIONS

1. The following approaches were helpful in the formulation of PVP-VA64 based ASD tablets
   - Mannitol as a filler, used in a ratio with MCC
   - Ac-di-sol as the disintegrating agent at a ~10% loading
   - Inclusion of formulation additives such as inorganic salts
2. We also found that modifying the following was beneficial
   - Filler type (Mannitol vs Dicalcium Phosphate)
   - Ratio of MCC: Filler
   - % Intragranular loading

Inorganic Salts- NaCl speeds disintegration time of tablets containing hydrophilic matrices

Fig 4. Effects of different independent variables on tableting CQA based on the screening DOE

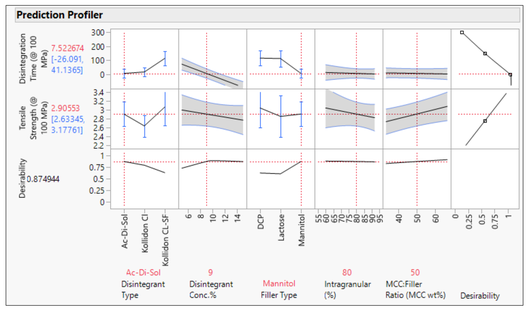


Table 2. Analysis of Variance results determining significance of different effects for response variables

Response	Effect Tests	P-value
Disintegration Time (min)	Disintegrant Type	0.0092
	% Disintegrant	0.0002
	Filler Type	0.0027
Tensile Strength (MPa)	MCC: Filler Ratio (% MCC)	0.0214

Fig 6. Hydrophilic matrix gelling phenomenon: **Impact of presence of inorganic salt in disintegration on hydrophilic tablet matrices:** Time series fluorescence images of hydrating HPMC matrix with (left) 0.008% w/v Congo Red and (right) NaCl with 0.008% w/v Congo Red

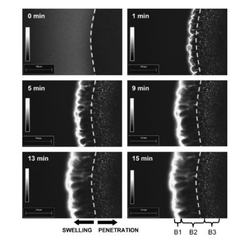


Figure 5. Time series of fluorescence images *in situ* of a hydrating HPMC matrix in aqueous 0.008% w/v Congo Red. For definitions of fluorescent regions B1, B2 and B3 refer to text. The images are coded for fluorescence intensity from white (highest) to black (lowest) as indicated by the wedge. The bright regions indicate areas of high fluorescence, highlighting regions of polymer hydration where the fluorophore has penetrated. Hydration medium maintained at 37°C. Ex 488/Em :- 510 nm. Scale bar :- 750 µm.

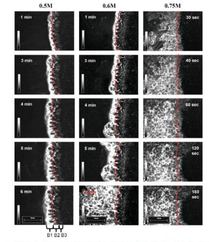
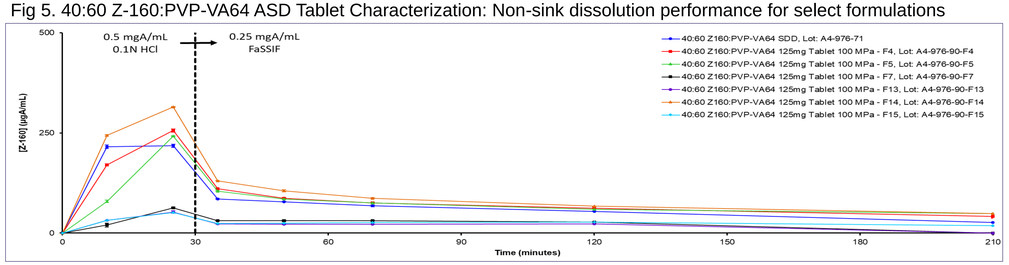


Figure 6. Time series of fluorescence images *in situ* of hydrating HPMC matrices in aqueous medium containing NaCl 0.5, 0.6 and 0.75 M and 0.008% w/v Congo Red. For definitions of fluorescent regions B1, B2 and B3 refer to text. The dashed line represents the initial tablet boundary at *t* : 0. The images are coded for fluorescence intensity from white (highest) to black (lowest) as indicated by the wedge. The bright regions indicate areas of high fluorescence, highlighting regions of polymer hydration where the fluorophore has penetrated. Hydration medium maintained at 37°C. Ex 488/Em :- 510 nm. Scale bar :- 750 µm.

Ref: Microstructural imaging of early gel layer formation in HPMC matrices, Journal of Pharmaceutical Sciences, Vol. 95, No. 10, October 2006

Fig 5. 40:60 Z-160:PVP-VA64 ASD Tablet Characterization: Non-sink dissolution performance for select formulations



Sample	Lot #	Total Drug C_{maxGB} (µgA/mL)	Total Drug $C_{maxFaSSIF}$ (µgA/mL)	Total Drug AUC $_{35\text{-}210\ FaSSIF}$ (min*µgA/mL)	Total Drug C_{210} (µgA/mL)	Disintegration time (min)
40:60 Z160:PVP-VA64 ASD	A4-976-71	218	85.6	9400	26.8	NA
40:60 Z160:PVP-VA64 125mg Tablet 100 MPa - F4	A4-976-90-F4	256	110.4	11200	41.8	~3
40:60 Z160:PVP-VA64 125mg Tablet 100 MPa - F5	A4-976-90-F5	242	105.1	11300	48.9	~20
40:60 Z160:PVP-VA64 125mg Tablet 100 MPa - F7	A4-976-90-F7	63	30.8	3800	0.0	>210
40:60 Z160:PVP-VA64 125mg Tablet 100 MPa - F13	A4-976-90-F13	53	23.1	3000	0.0	>210
40:60 Z160:PVP-VA64 125mg Tablet 100 MPa - F14	A4-976-90-F14	315	130.8	12800	49.1	~3
40:60 Z160:PVP-VA64 125mg Tablet 100 MPa - F15	A4-976-90-F15	52	27.0	4200	18.1	>210

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