PTR-099

Polyplasdone™ Ultra crospovidone for Oxidation-sensitive Drugs

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Introduction

Pharmaceutical products are a complex mixture of active pharmaceutical ingredients (APIs), excipients and impurities arising from both the API and excipients.[1] Hydrogen peroxide (H_2O_2) is one such impurity, induced by oxidative degradation of an API under accelerated conditions. Polyplasdone Ultra and Ultra-10 crospovidones low-impurity (30–50 ppm peroxide) superdisintegrants designed to be used in formulations of APIs sensitive to oxidative degradation. This study evaluated the effect of several superdisintegrants on impurity levels of the model oxidation-sensitive drugs clopidogrel bisulfate, fenofibrate, and atorvastatin. Superdisintegrants evaluated in this study were as follows:

- Polyplasdone crospovidone
- Competitive CL crospovidone
- Croscarmellose sodium
- Sodium starch glycolate

Because the XL and Ultra grades of Polyplasdone crospovidone have the same physical and chemical properties (the only difference being in the level of impurities) these grades are used interchangeably in this study. The competitive CL and CL-F grades of crospovidone vary only in particle size and are also used interchangeably.

Methods

Preparation of Clopidogrel Bisulfate Tablet by Direct Compression. The first four ingredients (Table 1) were passed through an 18 mesh screen, and blended for 10 minutes. A mixture of silicon dioxide and magnesium stearate was passed through a 35 mesh screen then blended with the first four ingredients. The final blend was compressed on a Manesty Betapress using 5/16” FFBE tooling, to a tablet weight of 240.2 mg. Tablet hardness, thickness, friability, and disintegration time were tested.

Note: This work was presented at the American Association of Pharmaceutical Scientists annual meeting, November 10–14, 2013, San Antonio, Texas.

Table 1. Clopidogrel bisulfate tablet formulation

Ingredients	Tablet formulation (% w/w)	Tablet weight (mg)
Clopidogrel bisulfate	40.8	98
Benecel™ A15LV methylcellulose	5	12.01
Lactose anhydrous	50.7	121.78
Superdisintegrant	2	4.8
Silicon Dioxide	0.5	1.2
Sodium stearyl fumarate	1	2.4
Total	100	240.2

Dissolution. Dissolution was carried out in 0.1N HCl, USP Apparatus II at 50 rpm for 30 minutes. Samples were withdrawn at 7.5, 15, and 30 minutes and filtered through a 0.45µm nylon membrane and quantitated by HPLC with UV detection at 220 nm. Column: Ultron ES-OVM Chiral, 4.6 x 150mm, Agilent 702111651.

Preparation of Orally Disintegrating Fenofibrate Tablets. Plasdone™ K29/32 povidone was dissolved in a quantity of DI water calculated to be 15% of batch size, then the sodium lauryl sulfate (SLS) was dissolved completely in the povidone solution. The remaining intragranular ingredients (Table 2) were passed through a 14 mesh screen. The screened materials were mixed for 2 minutes in the Collete high-shear mixer/granulator, then the povidone-SLS solution was sprayed in at 50 g/min, with the impeller at 295 RPM and chopper at 3554 RPM, until a suitable endpoint was achieved. The granulation was dried in an oven set to 65°C to NMT 2% moisture then passed through the FitzMill with a 0.065" screen, knives forward and medium speed. The milled fenofibrate granulation, each superdisintegrant and peppermint flavor were screened through an 18 mesh screen, and blended for 10 minutes. Magnesium stearate and silicon dioxide were passed through a 35 mesh screen, added to the blend and then blended for 3 minutes. The final blend was compressed on a Manesty Betapress using 3/8” FFBE tooling, to a tablet weight of 348 mg. Tablet hardness, thickness, friability, and disintegration time were tested.

Table 2. Fenofibrate tablet formulation

Ingredients	Tablet Formulation (% w/w)	Tablet Weight (mg)
Intragranular		
Fenofibrate	15.5	54
Mannitol	35	121.94
Microcrystalline cellulose	24	83.61
Sodium lauryl sulfate (SLS)	1.5	5.23
Plasdone™ K29/32 povidone	3	10.45
Extragranular		
Peppermint flavor	0.2	0.7
Superdisintegrant	20	69.68
Silicon dioxide	0.4	1.39
Magnesium stearate	0.4	1.39
Total	100	348.39

Dissolution of Fenofibrate Tablets. Dissolution was carried out in 0.05M sodium lauryl sulfate, USP Apparatus II at 75 rpm for 60 minutes. Samples were withdrawn at 15, 30, 45, and 60 minutes and immediately diluted with methanol to prevent precipitation of the fenofibrate from solution. The diluted samples were filtered through a 0.45 µm nylon membrane and quantitated by HPLC with UV detection at 286 nm. Column: Synergi 4 µm Hydro-RP 80Å, 250 × 4.6 mm.

Preparation of Orally Disintegrating Atorvastatin Tablets by Hot-melt Extrusion (HME). The first three ingredients in Table 3 were passed through a 20 mesh screen and blended for 10 minutes. The blend was extruded with the Leistritz 18 mm ZSE HP using processing parameters listed in Table 4. The extrudate was milled through the FitzMill with a 0.065" screen, knives forward and medium speed. The milled atorvastatin granulation, each superdisintegrant, aspartame and cherry flavor were screened through an 18 mesh screen, and blended for 10 minutes. Magnesium stearate and silicon dioxide were passed through a 35 mesh screen, added to the blend, and blended for 3 minutes. The final blend was compressed on a Manesty Betapress using 3/8" FFBE tooling, to a tablet weight of 300.69 mg. Tablet hardness, thickness, friability, and disintegration time were tested.

Table 3. Atorvastatin tablet formulation

Ingredients	Tablet Formulation (% w/w)	Tablet Weight (mg)
Intragranular		
Atorvastatin calcium trihydrate	7.2	21.65
Polyethylene glycol	1.8	5.41
Plasdone™ S-630 copovidone	9	27.06
Extragranular		
Calcium phosphate dibasic	45	135.31
Manitol	14	42.1
Superdisintegrant	20	60.14
Aspartame	1	3.01
Cherry flavor	0.5	1.5
Silicon dioxide	1	3.01
Magnesium stearate	0.5	1.5
Total	100	300.69

Table 4. Extruder processing temperatures and conditions

Extruder Process Temperatures								Extruder Process Conditions			
Zone 1	Zone 2	Zone 3	Zone 4	Zone 5	Zone 6	Zone 7	Zone 8	Feeder Speed (RPM)	Extruder Speed (RPM)	% Load	Melt Pressure (PSI)
40ºC	80ºC	110ºC	160ºC	170ºC	170ºC	165ºC	155ºC	100	200	37	344

Dissolution of Atorvastatin Tablets. Dissolution was carried out in phosphate buffer pH 6.8 using USP Apparatus II at 75 rpm for 45 minutes. Samples were withdrawn at 7.5, 15, and 30 minutes and immediately diluted with methanol to prevent precipitation of the atorvastatin from solution. The diluted samples were filtered through a 0.45 µm nylon membrane and quantitated by HPLC with UV detection at 270 nm. Column: ZORBAX Eclipse XDB-C8 3 mm × 150 mm, 5 µm.

Tablet Stability Protocol. All tablets were placed in 25°C/60%RH and 40°C/75% RH conditions without desiccant or tight sealed bottles. Samples were pulled at 1 month, 3 months and 6 months, and tested for drug release and impurities levels.

Results and Discussion

Clopidogrel Bisulfate Tablets. Clopidogrel bisulfate is an enantio-selective chiral drug and, to maintain activity, it needs to be protected from hydrolysis and oxidation in tablet formulations. The chemical structure of clopidogrel bisulphate (Figure 1) shows the dihydrothienopyridine group which contains an asymmetric carbon, leading to existence of two enantiomers (R and S). The active compound clopidogrel bisulfate is the S-enantiomer.[2] Therefore, under stressed conditions, clopidogrel can be transformed into the R-enantiomer, which, as an impurity, must be detected and monitored during stability studies, according to regulatory requirements.

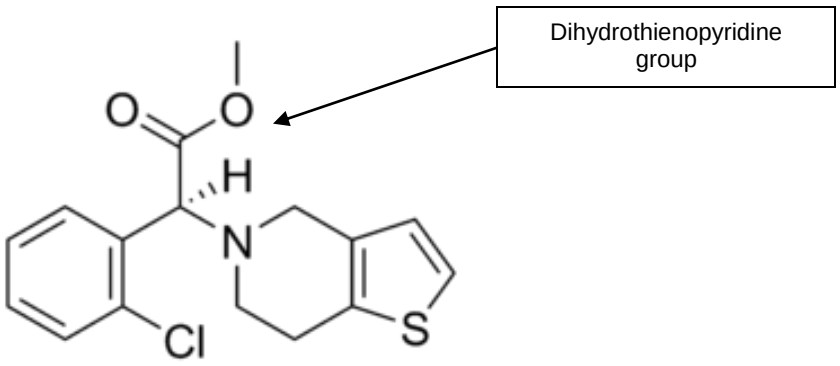


Figure 1. Chemical structure of clopidogrel bisulfate

Chromatographic assay[2] of the tablets from the stability study showed a retention time of 4.0–5.0 minutes for the active S-enantiomer, and 6.0–7.0 minutes for the impurity (R-enantiomer). Table 5 shows 6-month stability data for different formulations. Under stressed conditions, Clopidogrel bisulfate tablets made with Polyplasdone™ Ultra or Ultra-10 had the lowest total percent impurities and stayed within the USP acceptance limit (<3.0%), compared with the other tablets (Figure 2).

Table 5. Drug release and chemical stability of clopidogrel bisulfate tablets

Disintegrant	Initial		1 Month				3 Months				6 Months	
	Room Temp.		25°C/ 60% RH		40°C/ 75% RH		25°C/ 60% RH		40°C/ 75% RH		25°C/ 60% RH	
	% Drug release	% Impurities	% Drug release	% Impurities	% Drug release	% Impurities	% Drug release	% Impurities	% Drug release	% Impurities	% Drug release	% Impurities
Polyplasdone™ Ultra crospovidone	102.2	<0.1	101.6	<0.1	104.8	0.3	99.5	0.5	97.2	2.9	103.2	1.5
Polyplasdone™ Ultra-10 crospovidone	98.2	<0.1	103.1	<0.1	104.3	<0.1	99.3	0.8	100.0	2.1	103.1	1.7
Croscarmellose sodium	90.1	<0.1	100.2	0.8	100.1	1.5	85.5	1.4	85.3	6.0	100.7	2.0
Sodium starch glycolate	96.2	<0.1	102.6	1.06	90.2	9.4	86.9	1.4	88.8	7.5	103.2	2.3
Competitive equivalent CL crospovidone	96.5	<0.1	102.5	0.1	104.3	0.9	100.0	1.3	93.2	6.1	102.1	2.2
Competitive equivalent CL-F crospovidone	92.4	<0.1	101.4	0.4	93.0	10.2	95.3	1.8	97.0	5.9	101.9	2.3
Clopidogrel bisulfate only	94.4	<0.1	98.1	1.8	98.5	0.9	81.2	4.1	88.0	6.9	89.8	4.5

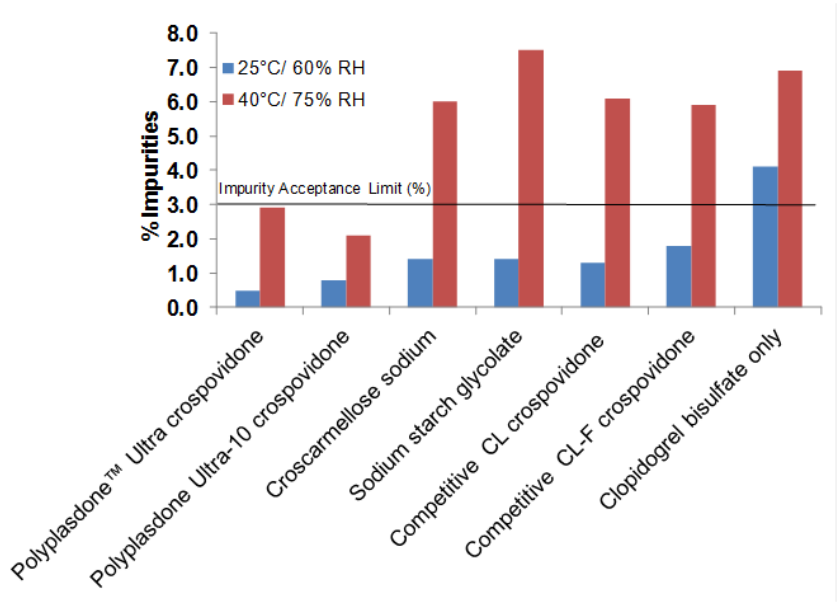


Figure 2. Total percent impurities of clopidogrel bisulfate tablets after 3 months

Orally Disintegrating Fenofibrate Tablets. Fenofibrate is an anti-hyperlipidemic agent which is moisture- and oxidation-sensitive. The structure of fenofibrate (shown in Figure 3), demonstrates that impurities can be produced by hydrolytic deesterification or oxidation.1

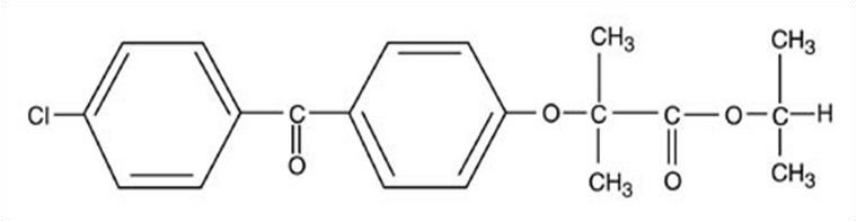


Figure 3. Chemical structure of fenofibrate

At initial testing, the fenofibrate tablets have an active peak at 19–20 minutes retention time;[3] no impurity peak was seen in any of the tablet formulations. The dissolution profiles of the initial fenofibrate tablets show that the tablets made with Polyplasdone™ Ultra crospovidones had the fastest drug release, when compared with the other tablets (Figure 4).

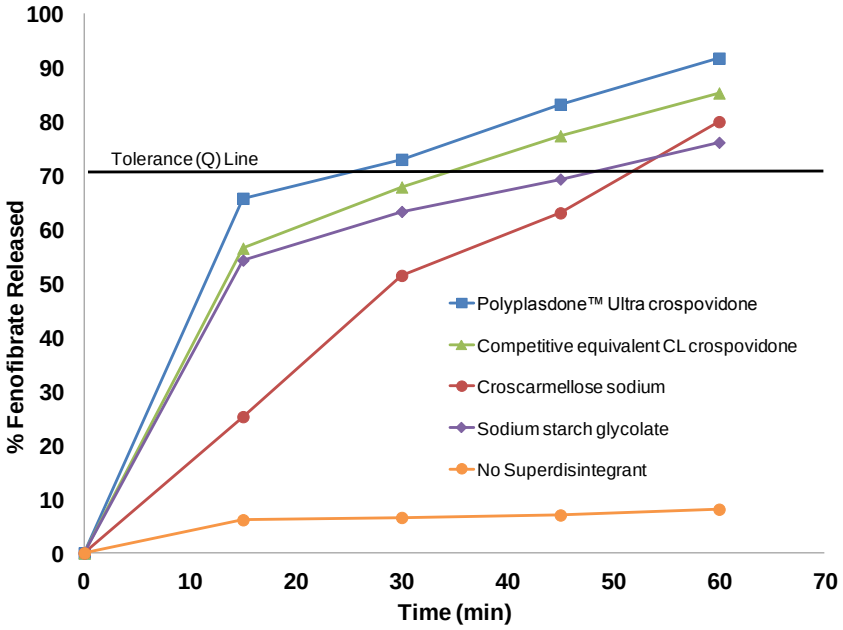


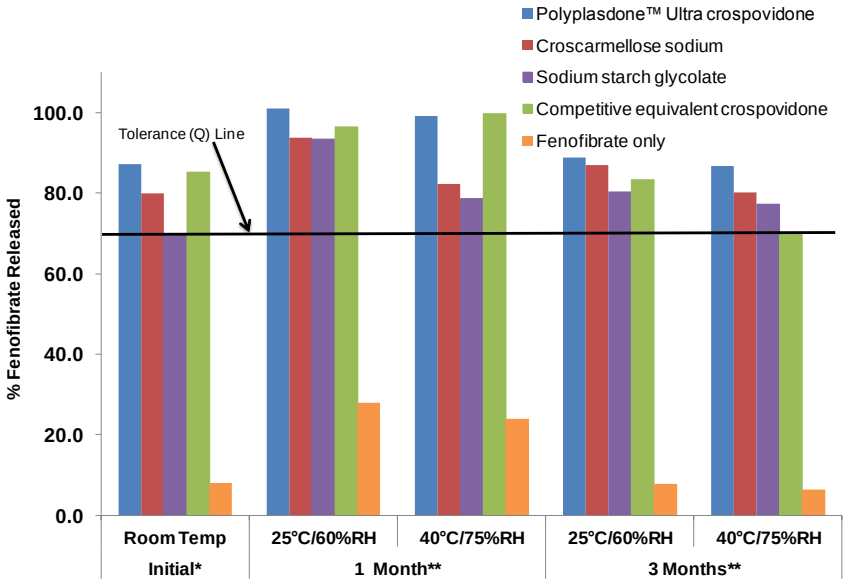
Figure 4. Dissolution profiles of fenofibrate (at initial time) in 0.025M sodium lauryl sulfate

After one month under stressed conditions, the impurities A and B were detected at retention times of 12 and 15 minutes, respectively.[3] Table 6 shows six months of stability data for fenofibrate tablets made with different superdisintegrants. Most tablets had percent drug releases within the USP Tolerance Q limit (70%) under accelerated stability conditions, over 3 and 6 months (Figure 5 and Table 6). However, total impurities data (Table 6 and Figure 6) have shown only tablets made with Polyplasdone Ultra crospovidones had the lowest total percent impurities, and stayed within the USP acceptance limit (≤1.0%), compared with the other tablets. Therefore, on the basis of the stability data, fenofibrate orally disintegrating tablets made with Polyplasdone™ Ultra crospovidones had better drug release and were more stable under stressed conditions than tablets made with other polymers (Figure 6). This suggests that Polyplasdone crospovidone retains less moisture than the other polymers, because fenofibrate is moisture sensitive.

Table 6. Percent drug release and impurities for fenofibrate tablets over six months

	Initial*		**1 Month****				**3 Months****				**6 Months****			
	Room Temp		25°C/60%RH		40°C/75%RH		25°C/60%RH		40°C/75%RH		25°C/60%RH		40°C/75%RH	
Disintegrant	% Drug Release	% Impurity	% Drug Release	% Impurity	% Drug Release	% Impurity	% Drug Release	% Impurity	% Drug Release	% Impurity	% Drug Release	% Impurity	% Drug Release	% Impurity
Polyplasdone™ Ultra crospovidone	87.1	<0.1	101.1	0.1	99.1	0.6	88.8	0.6	86.8	0.9	87.6	0.3	86.7	1.0
Croscarmellose sodium	80.0	<0.1	93.9	0.9	82.4	1.5	87.1	1.5	80.2	3.0	85.0	1.2	85.6	1.5
Sodium starch glycolate	69.6	<0.1	93.4	0.1	78.6	1.5	80.3	1.5	77.2	3.2	86.5	0.9	82.8	1.5
Competitive CL crospovidone	85.3	<0.1	96.4	0.6	99.8	1.2	83.3	1.2	70.0	2.4	81.8	1.6	80.7	1.4
Fenofibrate only	8.1	<0.1	28.0	0.1	23.9	1.6	7.7	1.6	6.4	1.3	2.8	0.2	6.7	0.2

Note. * Dissolution was performed in 0.025M SLS solution
** Dissolution was performed in 0.05M SLS solution



Note. * Dissolution was performed in 0.025M SLS solution
** Dissolution was performed in 0.05M SLS solution

Figure 5. Dissolution assay of fenofibrate tablets over three months

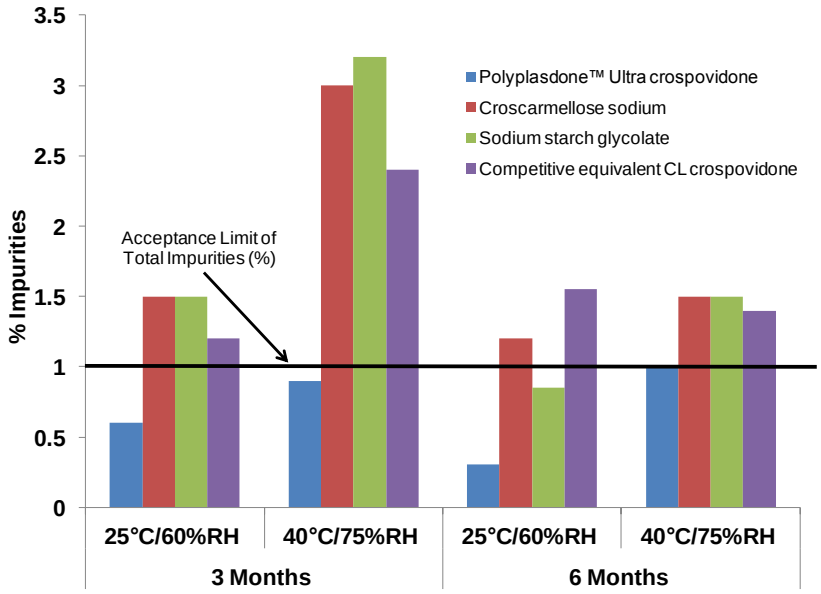


Figure 6. Impurities profiles for fenofibrate tablets over six months

Orally Disintegrating Atorvastatin Calcium Tablets. Atorvastatin calcium is a lipid-lowering agent, which is oxidation sensitive. Figure 7 shows the chemical structure of atorvastatin calcium, which is known to be subject to degradation under acidic and oxidative conditions.

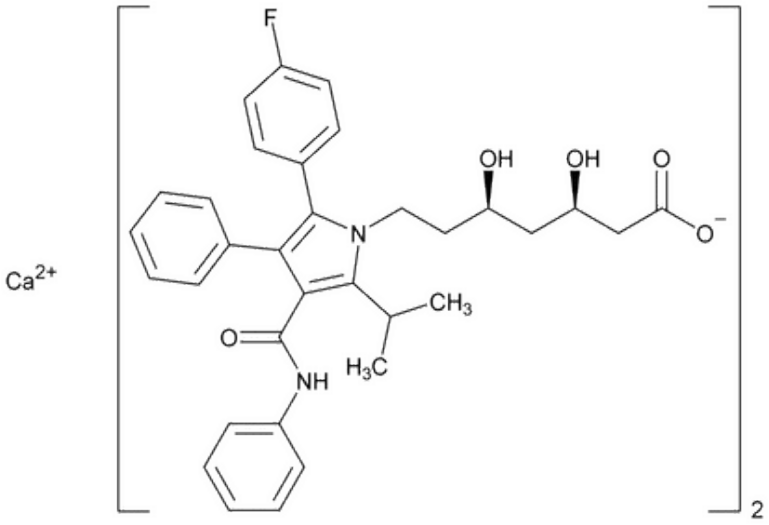


Figure 7. Chemical structure of atorvastatin calcium

The HPLC assay of the tablets from the stability study showed an active peak with a retention time of 1.9–2.2 minutes,[4] and an impurity peak at 2.6–2.8 minutes. Table 7 details the three month stability data for different formulations.

Table 7. Percent drug release and impurities for atorvastatin calcium tablets over three months

	Initial		1 Month				3 Months			
	Room Temp		25°C/60%RH		40°C/75%RH		25°C/60%RH		40°C/75%RH	
Disintegrant	% Drug Release	% Impurity	% Drug Release	% Impurity	% Drug Release	% Impurity	% Drug Release	% Impurity	% Drug Release	% Impurity
Polyplasdone™ Ultra crospovidone	95.3	0.5	91.9	0.2	90.8	0.4	99.3	0.2	100.0	0.8
Croscarmellose sodium	89.0	0.6	79.1	0.5	80.1	0.5	90.7	1.1	90.8	1.2
Sodium starch glycolate	94.7	0.8	86.2	0.9	85.1	0.6	86.4	1.3	98.3	1.2
Competitive CL crospovidone	92.1	0.8	78.0	0.5	75.9	0.5	88.8	0.9	95.5	1.2
Fenofibrate only	50.8	0.6	46.6	0.3	39.0	0.0	42.6	0.5	49.4	0.7

Under stressed conditions, most tablets had percent drug releases within the USP Tolerance Q limit (80%) under both accelerated stability conditions at three months (Figure 8). However, total impurities data (Table 7 and Figure 9) show tablets made with Polyplasdone™ Ultra crospovidones had the lowest total percent impurities compared with the other tablets.

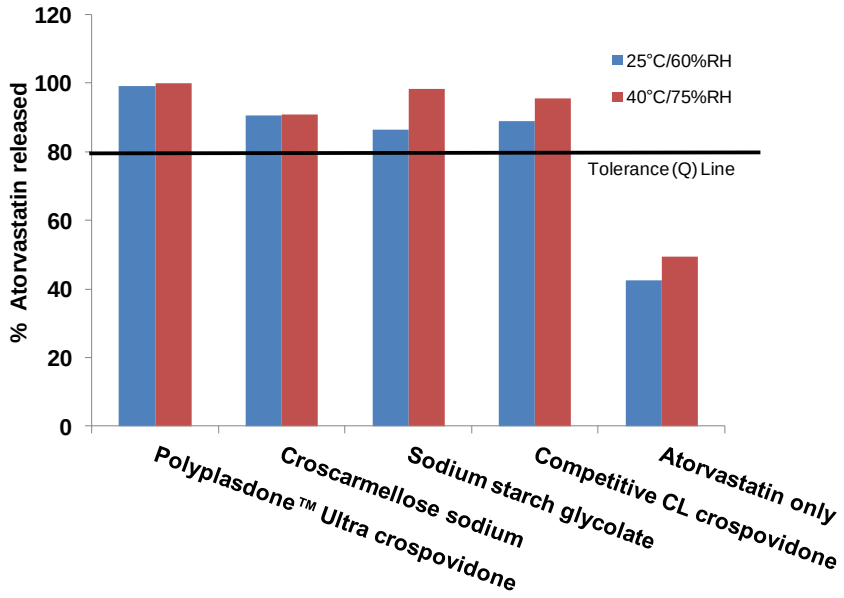


Figure 8. Dissolution assay of atorvastatin calcium tablets at three months

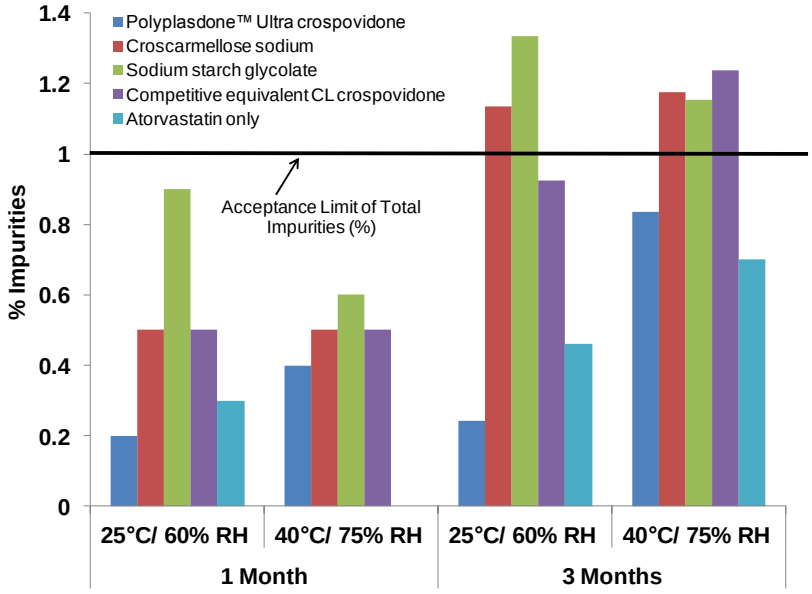


Figure 9. Impurities profiles for atorvastatin tablets over three months

Atorvastatin calcium tablets formulated with Polyplasdone Ultra crospovidone had the highest percent drug release, and lowest total percent impurities, compared with the other tablets.

Conclusions

Polyplasdone™ Ultra crospovidone, which has a very low peroxide level, can be used with oxidation-sensitive drugs. Under stressed conditions, Clopidogrel bisulfate and atorvastatin calcium tablets made with Polyplasdone Ultra had the lowest total percent impurities compared with the other tablets. Tablets formulated with fenofibrate (a moisture-sensitive drug) and Polyplasdone crospovidone show greater stability under stressed conditions than tablets made with other polymers. This suggests that Polyplasdone crospovidone has lower overall moisture and less adsorbed moisture than other superdisintegrants.

[1]Yue, Hongfei. Xin Bu, Ming-Hsing Huang, Joel Young, & Thomas Raglione. “Quantitative Determination of Trace Levels of Hydrogen Peroxide in Crospovidone and a Pharmaceutical Product using High Performance Liquid Chromatography with Coulometric Detection.” International Journal of Pharmaceutics, 375 (2009): 33–40.

[2]Yarkala, Sanjeeva, Sivakumar A, & Sameer G. Navalgund. “Physico-chemical Studies on Stability of Clopidogrel Tablet Formulations.” International Journal of Pharma and Bio Sciences, 3.4 (2012): 433–439.

[3]Lacroix, Pauline M., Brian A. Dawson, Roger W. Sears, D. Bruce Black, Terry D Cyr, & Jean-Claude Ethier. “Fenofibrate Raw Materials: HPLC Methods for Assay and Purity and an NPR Method for Purity.” Journal of Pharmaceutical and Biomedical Analysis, 18 (1998): 383–402.

[4]Ramesha, B., K.R. Venugopala Reddy, B. V. Kishore, M. K. Amith Kumar, L. P. Raju, & B. N. Thara. “Development and Validation of Stability-indicating Gradient RP-UHPLC Method for the Determination of Impurities in Atorvastatin Drug Subtance.” Journal of Liquid Chromatography and Related Technologies, 37.3 (2014): 275–297.