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SUPPLEMENTARY MATERIAL TO

Application of gas chromatography analysis to quality control of residual organic solvents in clopidogrel bisulfate

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TABLE S-I. USP class,[1] USP[1] and in-house specification limits

Solvent name	USP class	USP specifications, μg g^{-1}	In house specifications, μg g^{-1}
Cyclohexane	2	3880	2000
DMF	2	880	880
Methanol	2	3000	500
DCM	2	600	600
Toluene	2	890	890
Acetic acid	3	5000	2600
Acetone	3	5000	500
2-Butanol	3	5000	5000
1-Butene	4	No data	450
2-Butene	4	No data	3500
Dibutyl ethers	4	No data	700

TABLE S-II. Results of the analysis of 18 batches of clopidogrel bisulfate

Compound	CU1 005 B 07	AAEH0 04042	AACH0 02419	AABH0 02053	AABH0 03050	AACH0 00141	AADH0 02533	AACH0 04351	AACH0 04331
Cyclohexane	1228	*<LOD*	*<LOD*	1315	1349	*<LOD*	735	*<LOD*	*<LOD*
DMF	*<LOD*	*<LOD*	*<LOD*	*<LOD*	45	*<LOQ*	*<LOD*	*<LOD*	*<LOD*
Methanol	*<LOD*	*<LOD*	*<LOD*	*<LOD*	26	*<LOD*	*<LOQ*	*<LOD*	*<LOD*
DCM	43	*<LOD*	*<LOD*	*<LOD*	*<LOD*	*<LOD*	*<LOD*	*<LOD*	*<LOD*
Toluene	*<LOQ*	*<LOQ*	*<LOD*	*<LOD*	*<LOD*	*<LOD*	*<LOD*	*<LOD*	*<LOD*
Acetic acid	1449	924	694	996	238	353	2186	*<LOD*	462

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TABLE S-II. Continued

Compound	CU1 005 B 07	AAEH0 04042	AACH0 02419	AABH0 02053	AABH0 03050	AACH0 00141	AADH0 02533	AACH0 04351	AACH0 04331
Acetone	<*LOQ*	<*LOQ*	<*LOD*	<*LOD*	<*LOD*	<*LOD*	<*LOD*	683	<*LOD*
2-Butanol	1306	506	107	<*LOQ*	156	<*LOQ*	188	188	104
1-Butene	174	220	450	176	325	180	193	282	311
2-Butene	1261	1832	2369	2653	1763	1600	1706	2418	2659
Dibutyl ethers	372	251	277	335	306	210	247	258	289
	AACH004 382	AACH0 05313	AACH0 06029	AADH0 01338	AADH0 02376	AADH0 02533	AADH0 04826	AADH0 04485	AADH0 04164
Cyclohex-ane	<*LOD*	<*LOD*	<*LOD*	<*LOD*	<*LOQ*	173	<*LOD*	<*LOQ*	<*LOD*
DMF	<*LOD*	<*LOD*	<*LOD*	<*LOD*	<*LOD*	<*LOD*	<*LOD*	<*LOD*	<*LOD*
Methanol	<*LOD*	<*LOD*	28	<*LOD*	<*LOD*	<*LOQ*	32	41	<*LOD*
DCM	<*LOD*	<*LOD*	<*LOD*	<*LOD*	<*LOQ*	<*LOQ*	<*LOD*	<*LOD*	<*LOD*
Toluene	<*LOD*	<*LOD*	<*LOQ*	<*LOD*	<*LOD*	<*LOD*	<*LOQ*	<*LOQ*	<*LOD*
Acetic acid	766	666	372	456	1257	610	195	<*LOD*	683
Acetone	<*LOD*	<*LOD*	<*LOD*	<*LOD*	<*LOD*	<*LOD*	<*LOD*	47	<*LOD*
2-Butanol	387	998	1486	<*LOQ*	<*LOQ*	180	433	248	88
1-Butene	215	116	87	236	197	266	227	272	282
2-Butene	1946	880	641	2323	1826	2420	1750	2281	2418
Dibutyl ethers	349	317	251	284	298	337	239	306	258

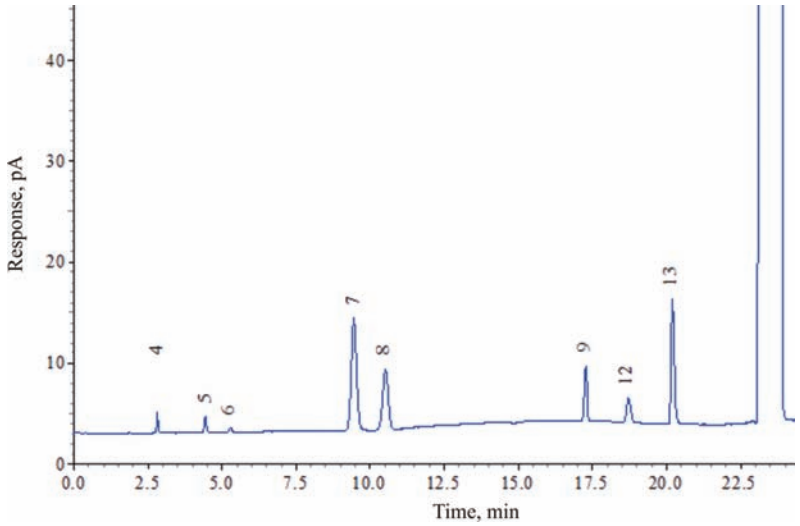

Fig. S-1. Chromatogram of the standard solution. Peaks marked with numbers belong to the following solvents: 4) methanol, 5) acetone, 6) DCM, 7) 2-butanol, 8) cyclohexane, 9) toluene, 12) acetic acid and 13) DMF.

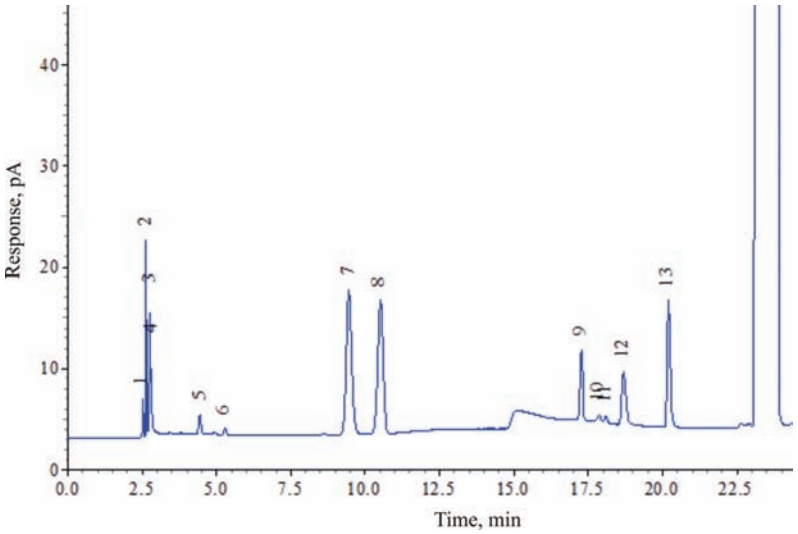

Fig. S-2. Chromatogram of the test solution spiked with residual solvents at the level of specifications. Peaks marked with numbers belong to the following solvents: 1) 1-butene, 2) *trans*-2-butene, 3) *cis*-2-butene, 4) methanol, 5) acetone, 6) DCM, 7) 2-butanol, 8) cyclohexane, 9) toluene, 10) 2,2′-oxybis[butane], 11) 1-(1-methylpropoxy)butane, 12) acetic acid and 13) DMF.

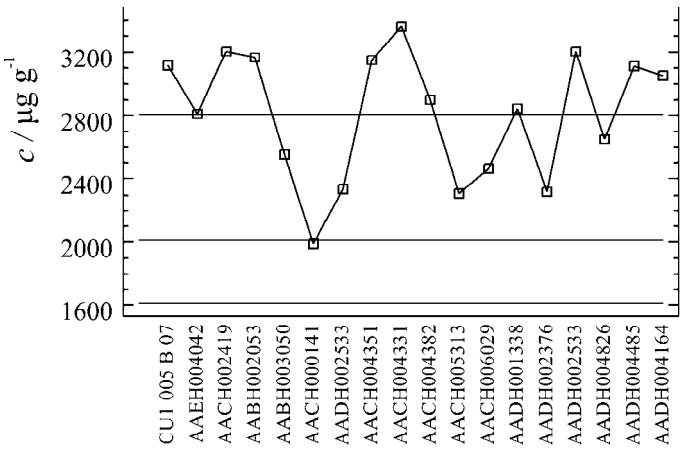

Fig. S-3. The means of the sum of 2-butanol and its dehydration products (2806.0 µg g^{-1}) for the 18 different batches and lower control limits (*LCL* = 1612.0 µg g^{-1}). Lower warning limit, at 2010 µg g^{-1}, is represented as two standard errors.

REFERENCES

1. *The United States Pharmacopeia–National Formulary*, US Pharmacopeial Convention, Rockville, MD, 2013, p. 5707