

Physicochemical Stability of diluted "Akynzeo®" Infusion Solutions in prefilled 0.9% Sodium Chloride Infusion Bags

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Background and Importance

Akynzeo® 235 mg/0.25 mg concentrate for solution for infusion, indicated for prevention of acute and delayed chemotherapy-induced nausea and vomiting, contains a combination of fosnetupitant (FOS) and palonosetron (PAL). Prior to administration, the Akynzeo® concentrate (20 mL vial) is diluted with either 30 mL or 100 mL 0.9% sodium chloride infusion solution. According to the SmPC, ready-to-administer (RTA) infusion solutions are physicochemically stable for 24 hours stored at room temperature [1].

Aim and Objectives

The aim of the study was to determine the **long term physicochemical stability** of two different ready-to-administer FOS/PAL infusion solutions in polyolefin (PO) infusion bags **stored at room temperature over a 14-day period**.

Materials and Methods

Preparation of test solutions: FOS/PAL (Akynzeo® 235 mg/0.25 mg injection solution, 20 mL) diluted with 0.9% sodium chloride in prefilled PO bags

FOS/PAL Bag A
 20 mL Akynzeo®
 + 30 ml 0.9% sodium chloride

Single samples withdrawn immediately (h0) and at day 0.5, 1, 2, 3, 5, 14

FOS/PAL Bag B
 20 mL Akynzeo®
 + 100 ml 0.9% sodium chloride

- **Validated:** according to ICH Q2 (R1) Guideline
- **Detector:** PDA at 228 nm
- **Column:** Thermo Scientific Synchronis C18, 5µm, 250 x 4.6 mm
- **Mobile phase A:** sodium perchlorate buffer 1% (pH 6.6)
- **Mobile phase B:** acetonitrile HPLC grade
- **Injection volume:** 20 µL (in triplicate)
- **Flow Rate:** 1.0 ml/min

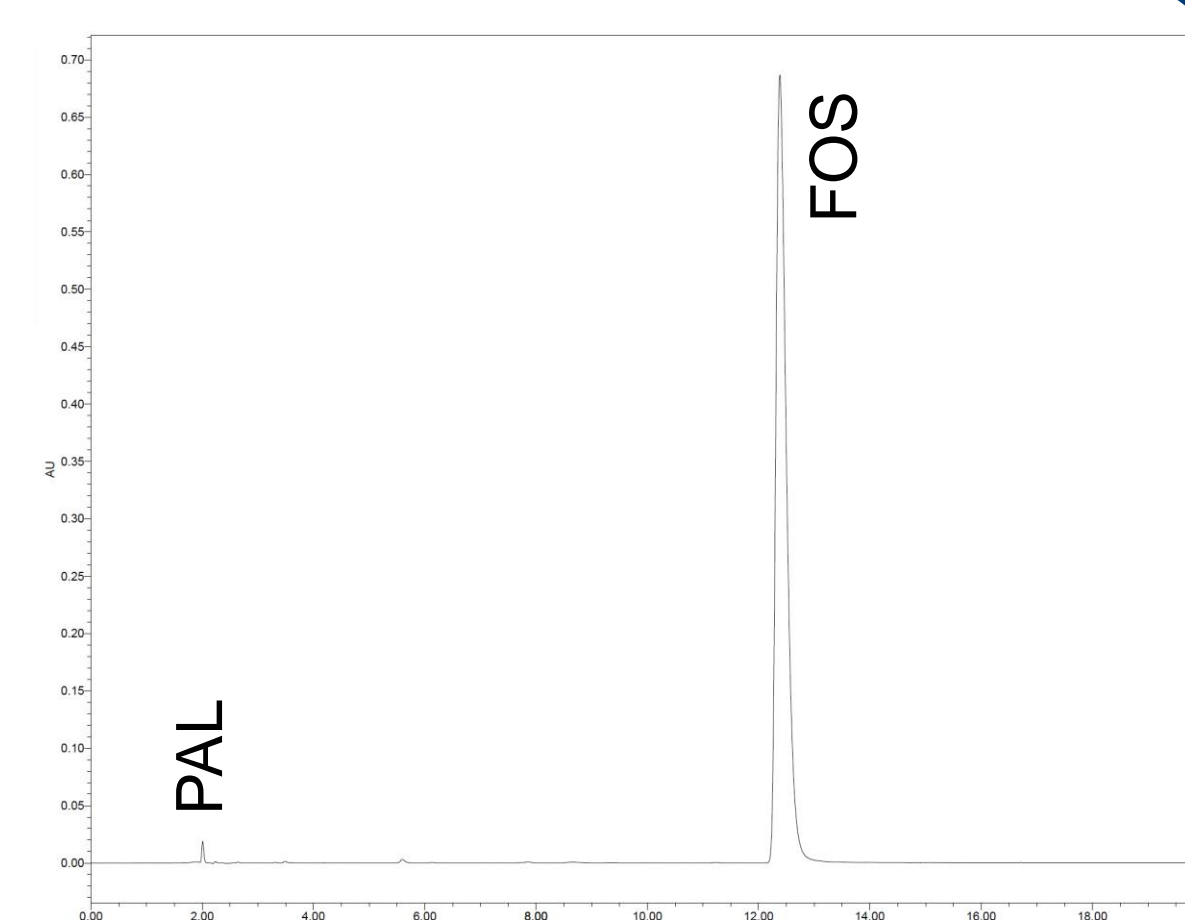
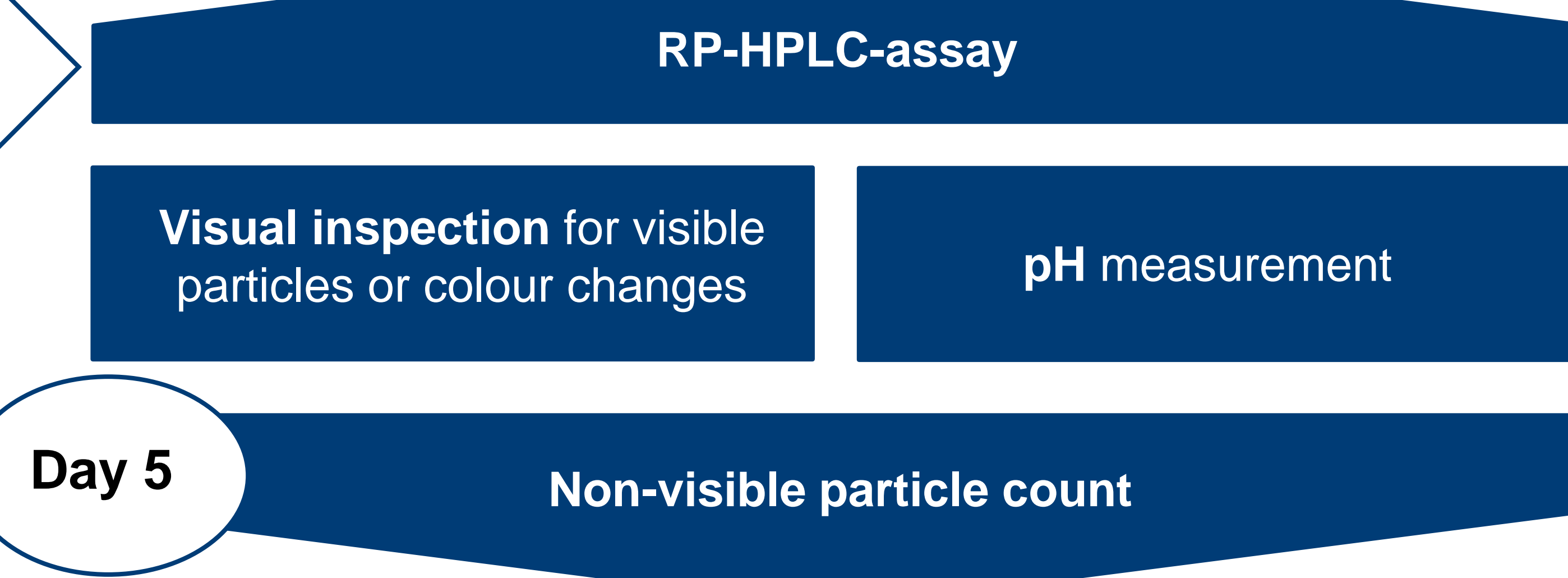


Fig. 1: RP-HPLC chromatogram of PAL and FOS



- **Specification:** according to Ph. Eur. 2.9.19
- $\geq 10 \mu\text{m}$: ≤ 6000 particles / bag
- $\geq 25 \mu\text{m}$: ≤ 600 particles / bag

Results

Tab. 1: FOS concentration in FOS/PAL test bag A, stored at 25 °C over 14 days.

Test bag	Nominal FOS concentration 4.70 mg/mL						
	Measured FOS concentration [mg/mL]						
	Day						
	0	0.5	1	2	3	5*	14
Bag A1	4.86	4.83	4.80	4.82	4.82	(4.62)	4.89
	4.88	4.83	4.80	4.83	4.83	(4.60)	4.91
	4.85	4.82	4.82	4.83	4.82	(4.60)	4.90
Bag A2	4.91	4.81	4.83	4.77	4.86	(4.62)	4.88
	4.90	4.81	4.83	4.77	4.86	(4.60)	4.88
	4.90	4.80	4.83	4.77	4.85	(4.59)	4.87
Bag A3	4.81	4.73	4.83	4.84	4.79	(4.47)	4.89
	4.81	4.73	4.83	4.83	4.79	(4.48)	4.88
	4.80	4.71	4.84	4.81	4.79	(4.45)	4.88
Mean [mg/mL] (n=9)	4.86	4.79	4.82	4.81	4.82	(4.56)	4.89
Percentage rate initial concentration [%]	100.00**	98.50	99.29	98.94	99.29	(93.83)	100.57
SD [mg/mL]	0.0404	0.0451	0.0130	0.0292	0.0281	(0.0659)	0.0116
RSD [%]	0.83	0.94	0.27	0.61	0.58	(1.45)	0.24

Tab. 5: FOS concentration in FOS/PAL test bag B, stored at 25 °C over 14 days.

Test bag	Nominal FOS concentration 1.96 mg/mL						
	Measured FOS concentration [mg/mL]						
	Day						
	0	0.5	1	2	3	5*	14
Bag B1	1.97	1.90	1.95	1.93	1.94	(1.79)	1.98
	1.98	1.90	1.95	1.93	1.94	(1.78)	1.98
	1.97	1.90	1.95	1.93	1.94	(1.77)	1.97
Bag B2	1.93	1.91	1.94	1.92	1.92	(1.77)	1.98
	1.93	1.91	1.94	1.92	1.91	(1.76)	1.97
	1.93	1.90	1.94	1.91	1.91	(1.74)	1.97
Bag B3	1.95	1.90	1.92	1.93	1.94	(1.74)	1.97
	1.95	1.89	1.93	1.93	1.94	(1.73)	1.97
	1.94	1.88	1.92	1.92	1.93	(1.72)	1.97
Mean [mg/mL] (n=9)	1.95	1.90	1.94	1.92	1.93	(1.75)	1.97
Percentage rate initial concentration [%]	100**	97.29	99.40	98.68	99.00	(89.97)	101.14
SD [mg/mL]	0.0179	0.0085	0.0115	0.0062	0.0106	(0.0216)	0.0035
RSD [%]	0.92	0.45	0.59	0.32	0.55	(1.23)	0.18

Tab. 2: PAL concentration in FOS/PAL test bag A, stored at 25 °C over 14 days.

Test bag	Nominal PAL concentration 5.00 µg/mL						
	Measured PAL concentration [µg/mL]						
	Day						
	0	0.5	1	2	3	5	14
Bag A1	5.55	5.81	5.32	5.44	5.39	5.25	5.42
	5.55	5.78	5.34	5.46	5.45	5.37	5.42
	5.55	5.78	5.36	5.47	5.44	5.42	5.41
Bag A2	5.87	5.65	5.51	5.48	5.63	5.47	5.41
	5.85	5.67	5.53	5.51	5.63	5.48	5.44
	5.84	5.67	5.55	5.54	5.65	5.48	5.41
Bag A3	5.35	5.42	5.45	5.50	5.51	5.36	5.34
	5.34	5.43	5.46	5.51	5.50	5.38	5.32
	5.34	5.41	5.46	5.52	5.51	5.39	5.34
Mean [µg/mL] (n=9)	5.58	5.62	5.44	5.49	5.52	5.40	5.39
Percentage rate initial concentration [%]	100.00*	100.73	97.48	98.36	98.94	96.78	96.54
SD [µg/mL]	0.2090	0.1552	0.0798	0.0287	0.0879	0.0682	0.0419
RSD [%]	3.74	2.76	1.47	0.52	1.59	1.26	0.78

Tab. 6: PAL concentration in FOS/PAL test bag B, stored at 25 °C over 14 days.

Test bag	Nominal PAL concentration 2.08 µg/mL						
	Measured PAL concentration [µg/mL]						
	Day						
	0	0.5	1	2	3	5	14
Bag B1	2.39	2.29	2.20	2.26	2.30	2.19	2.24
	2.36	2.29	2.20	2.25	2.30	2.19	2.24
	2.35	2.29	2.20	2.25	2.30	2.19	2.24
Bag B2	2.25	2.34	2.17	2.23	2.18	2.20	2.24
	2.21	2.33	2.18	2.22	2.18	2.20	2.24
	2.21	2.33	2.17	2.22	2.19	2.20	2.24
Bag B3	2.18	2.30	2.21	2.27	2.26	2.20	2.31
	2.18	2.28	2.21	2.27	2.25	2.21	2.31
	2.18	2.28	2.21	2.27	2.24	2.22	2.31
Mean [µg/mL] (n=9)	2.26	2.30	2.19	2.25	2.24	2.20	2.26
Percentage rate initial concentration [%]	100.00*	102.11	97.28	99.72	99.41	97.33	100.37
SD [µg/mL]	0.0805	0.0219	0.0164	0.0186	0.0472	0.0096	0.0342
RSD [%]	3.57	0.95	0.75	0.83	2.10	0.44	1.51

Tab. 3: pH values of FOS/PAL test bag A, stored at 25 °C over 14 days.

Test bag	20 mL Akynzeo® + 30 mL 0.9% sodium chloride						
	pH value						
	Day						
	0	0.5	1	2	3	5	14
Bag A1	6.85	6.95	6.93	6.77	6.81	7.24	ND
Bag A2	7.10	7.01	7.11	7.01	6.97	7.17	ND
Bag A3	7.37	7.12	7.08	6.99	7.27	ND	ND

Tab. 4: Non-visible particles of FOS/PAL test bag A, stored at 25 °C.

Test bag	20 mL Akynzeo® + 30 mL 0.9% sodium chloride solution	
	Number [n] of non-visible particles on day 5	
	$\geq 10 \mu\text{m}$	$\geq 25 \mu\text{m}$
Bag A1	6381*	32
Bag A2	4632	21
Bag A3	2240	16

Tab. 7: pH values of FOS/PAL test bag B, stored at 25 °C over 14 days.

Test bag	20 mL Akynzeo® + 100 mL 0.9% sodium chloride						
	pH value						
	Day						
	0	0.5	1	2	3	5	14
Bag B1	6.95	6.98	7.00	6.93	6.79	6.82	ND
Bag B2	6.85	6.96	6.97	6.90	6.73	6.78	ND
Bag B3	6.76	6.96	6.91	6.85	6.72	6.94	ND

Tab. 8: Non-visible particles of FOS/PAL test bag B, stored at 25 °C.

Test bag	20 mL Akynzeo® + 100 mL 0.9% sodium chloride solution	
	Number [n] of non-visible particles on day 5	
	$\geq 10 \mu\text{m}$	$\geq 25 \mu\text{m}$
Bag B1	3820	67
Bag B2	2253	13
Bag B3	2753	7

➤ **Visual inspection:** solutions of FOS/PAL test bags A and test bags B remained clear, without change of color or appearance of visible particles over 14 days.

Conclusion

Ready-to-administer FOS/PAL infusion solutions (Akynzeo® 235 mg/0.25 mg concentrate for solution for infusion) diluted with 30 mL and 100 mL in prefilled 0.9 % sodium chloride PO bags are physicochemically stable up to **14 days when stored at 25 °C** and protected from light.

References

[1] Akynzeo Summary of product characteristics. https://www.ema.europa.eu/en/documents/product-information/akynzeo-epar-product-information_en.pdf