Physicochemical stability of sufentanil citrate in Rythmic™ administration set reservoirs or in a polyolefin infusion bag diluted in 0.9% sodium chloride or in 5% dextrose at 1 and 10 µg/mL stored at 20-25°C protected from light

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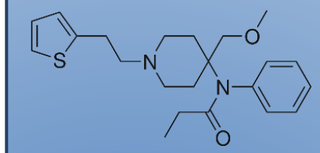
Introduction

Sufentanil citrate → high capacity of sorption onto surfaces containing polyvinylchloride (PVC) with bis(2-ethylhexyl) phthalate (DEHP) or polypropylene (PP).[1, 2]

To our knowledge, there aren't stability studies of sufentanil citrate solutions in PVC containers without DEHP.

What is the capacity of sorption of sufentanil citrate onto Rythmic™ administration set reservoir bag made of polyvinyl chloride (PVC) **without DEHP**?



Objectives

① Study the **physicochemical stability of sufentanil citrate**

② Investigate the **potential sorption phenomena** onto Rythmic™ reservoir bag (DEHP-free PVC)

Materials and Method

Chemical stability

① **Conditions:**

- Concentrations = 1 and 10 µg/mL
- Containers :
  - polyolefin bags (Easyflex®, Freeflex®) = POF
  - Rythmic™ administration set reservoir (DEHP-free PVC) =
- Solvent = 0.9% sodium chloride (0.9% NaCl); 5% dextrose (D5W)
- Storage = 20-25°C, protected from light
- Analysis = on days 0, 3 and 7

/ condition

② **Method:** HPLC-DAD detector at 238 nm

- Column: LiChrospher® 100 - RP-18, 12.5 cm , particle size = 5 µm
- Mobile phase: isocratic elution *(buffer solution (ultrapure water + ammonium acetate at 10 g/L adjusted at pH=7 with NaOH 0.1M), methanol, acetonitrile for HPLC at 31/45/24)*
- Flow rate: 1.5 mL/min
- Injection volume: 99 µL
- Analysis time: 10 min

③ **Validation of the analytical method** as recommended by ICH Q2(R1)

- Forced degradation:

Acidic	HCl 0.1M (4h, 90°C)
Alkaline	NaOH 0.1M (4h, 90°C)
Oxydative	H_2O_2 3%
Photolytic	UV (24h at 254 nm)
Heat	8h at 90°C

- Linearity: standard curve with 5 points (0.5 - 20 µg/mL)
- Repeatability and intermediate precision: 3-point measurement (0.5, 10 and 20 µg/mL) on 3 different days
- Specificity

③ **pH measurement** (CRISON pH25 pH-meter) : on days 0, 3 and 7

Physical stability

① **Visual examination**: change of colour, precipitation, gas formation

② **Subvisual examination**: PAMAS particle counter

Acceptability criteria: Ph. Eur. 2.9.19. «Particulate contamination: sub-visible particles»

Particles per mL	
≥ 10 µm	≥ 25 µm
25	3

Acceptability criteria

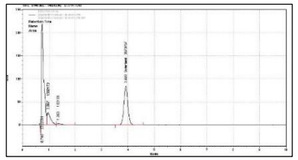
± 10% of initial concentration and no visual or significative pH value modification

Results

① **Validation: HPLC method**

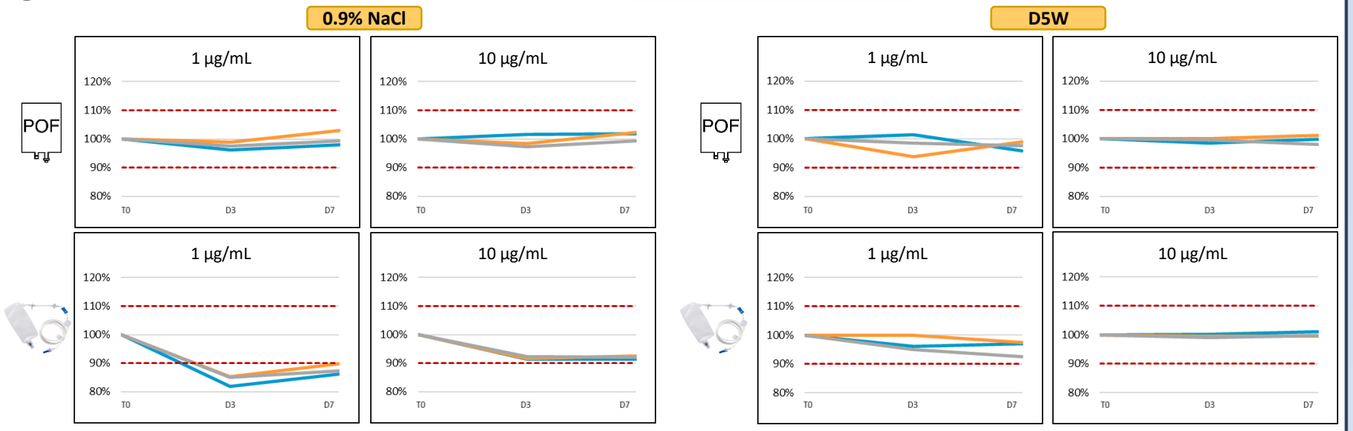
- Linearity: $R^2 > 0.999$
- Repeatability: < 2%
- Intermediate precision: < 4%
- Retention time: 3.96 min

- Stability indicating capacity: degradation up to 19%, degradation products separated from sufentanil



Chromatogram of sufentanil citrate solution at 10 µg/mL after alkaline degradation (NaOH 0.1 M, 4h, 90°C)

② **Chemical stability – HPLC**



pH measurements: maximum variation ±0.22 pH unit on D7

③ Physical stability

Visual and subvisual examination: no change detected

Conclusion

✓ **Solutions of sufentanil citrate → stable for 7 days at 20-25°C**

PVC without DEHP	◆	1 µg/mL 10 µg/mL	20-25°C	7 days
	▲	10 µg/mL		
POF	▲ ◆	1 µg/mL 10 µg/mL		

◆ D5W ▲ 0.9% NaCl

⚠ **Except → 1 µg/mL, 0.9% NaCl, Rythmic™**

- > 10% concentration loss on D3, stable on D7
- Solvent impact
- pH significance
- Only low concentration solution affected

Sorption phenomenon hypothesis

[1] Westphal M, Hohage H, Buerkle H, Van Aken H, Ermert T, Brodner G. sorption of sufentanil to epidural filters and catheters
[2] Roos PJ, Glerum JH, Schroeders MJH. Effect of glucose 5% solution and bupivacaine hydrochloride on absorption of sufentanil citrate in a portable pump reservoir during storage and simulated infusion by an epidural catheter