COMPATIBILITY AND STABILITY OF MORPHINE AND FUROSEMIDE ADMIXTURES

OHP-048

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BACKGROUND

In order to avoid separate injections of different drugs, admixtures of opioids with other drugs used in palliative care are frequently used. There are different factors that can influence the compatibility and stability of the mixture: drug type, concentration, solvent, container, temperature and light. There are some mixtures of opioids with other drugs with proven stability, but there is lack of evidence about the stability and compatibility of the combination of morphine and furosemide.

PURPOSE

To evaluate the compatibility and stability of the admixture morphine 1.0 mg/ml - furosemide 0.6 mg/ml in NaCl 0.9% stored at ambient room temperature under normal light for at least 30 days. Also, to study the stability of this admixture stored in infuser.

METHOD

On study day 0, a mixture was prepared and diluted in NaCl 0.9% to obtain 1.0 mg/ml of morphine and 0.6 mg/ml of furosemide and stored at ambient room temperature under normal light.

The concentration of the mixture was periodically determined by using a HPLC-UV method. Dilution of the sample was made prior to the analysis to give 40 mg/mL of morphine and 24 mg/mL of furosemide. Five standards were prepared all days of the study

RESULTS

• Preliminary study:

λ= 235 nm ; Stationary phase: C18
Flow rate: 0.7 mL/min
Mobile phase: Acetonitrile:Water (40:60)
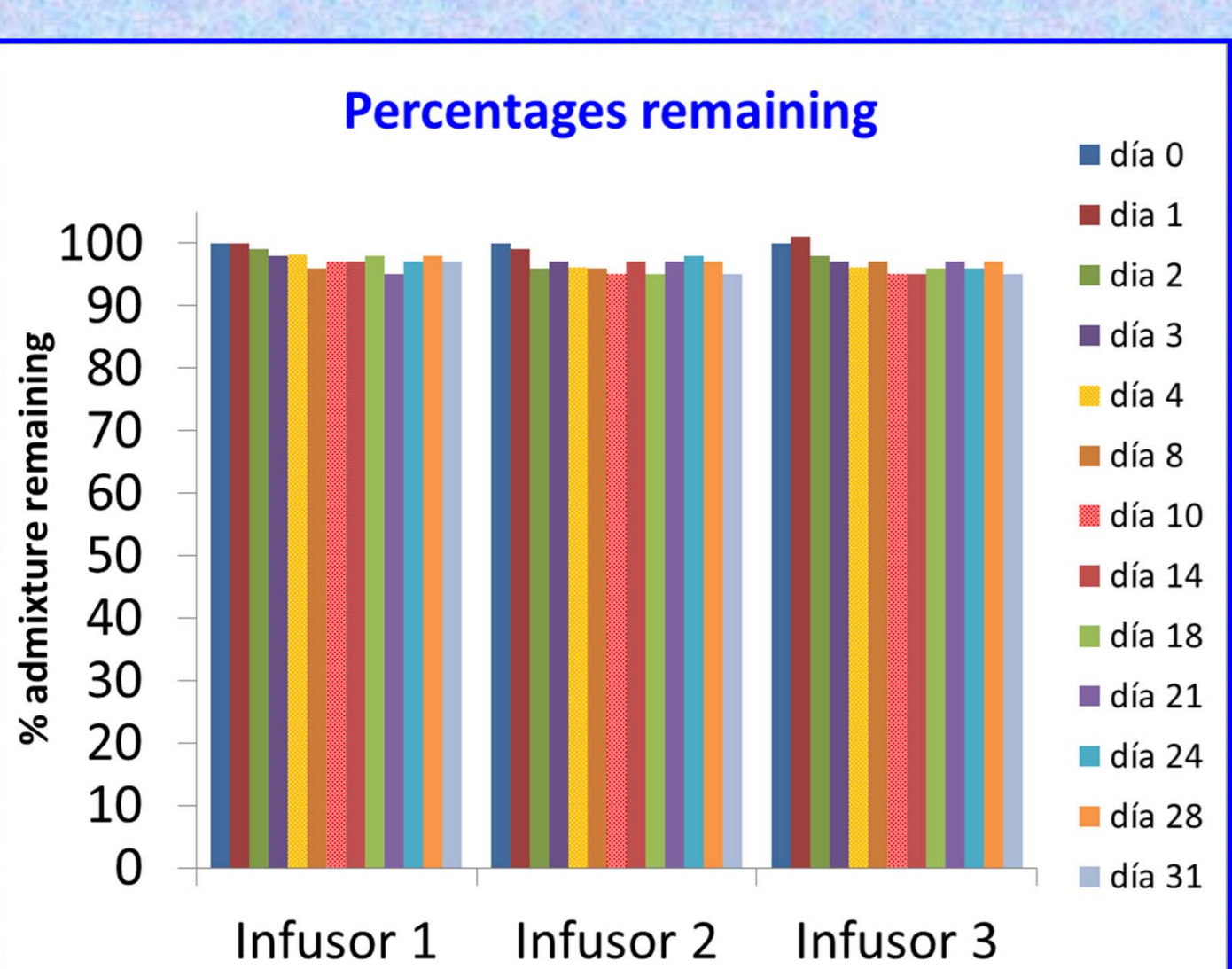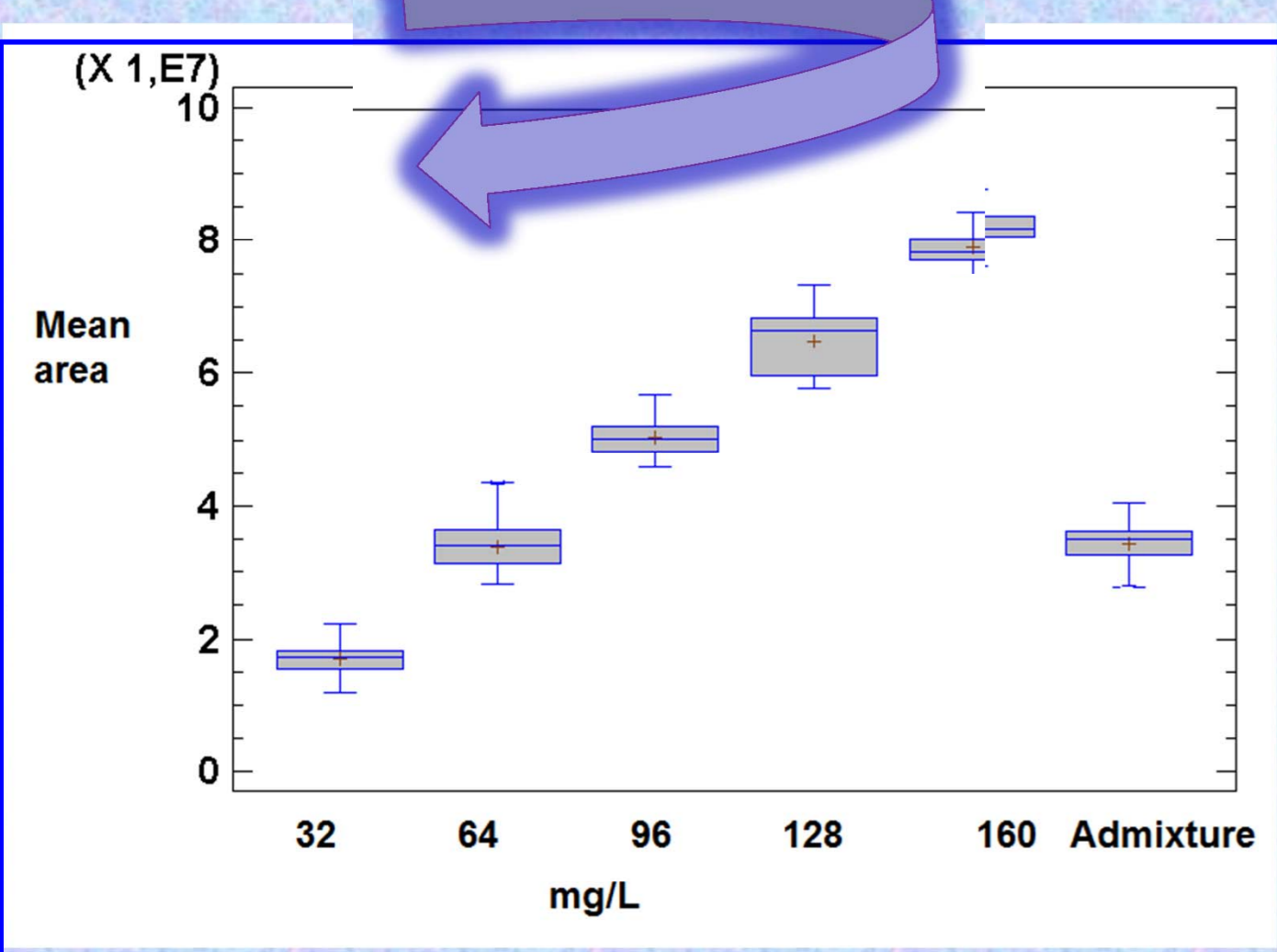Rt (morphine): 2.8 min; Rt (furosemide): 3.6 min

Study day	MOR mg/L ± SD	FUR mg/L ± SD	Recovery % MORPHINE	Recovery % FUROSEMIDE
0	38.25 ± 1.46	22.16 ± 0.26	96.3	92.33
1	39.89 ± 1.90	22.40 ± 0.06	99.73	93.33
2	37.42 ± 2.08	21.22 ± 0.89	93.55	88.42
3	38.81 ± 3.06	22.11 ± 0.11	97.03	92.13
8	37.64 ± 3.07	21.87 ± 0.15	94.1	91.13
9	39.04 ± 4.56	21.37 ± 0.60	97.6	89.04
10	38.86 ± 0.39	21.72 ± 1.06	97.15	90.5

Flow rate: 1.5 mL/min
Mobile phase: Acetonitrile:Water (80:20)

Study day	Admixture (mg/L ± SD)	Recovery %
0	63.5 ± 2.2	99.2
1	64.4 ± 1.6	100.6
2	66.7 ± 0.6	104.2
5	65.1 ± 1.2	101.7
7	64.9 ± 1.2	101.4
9	60.3 ± 0.9	94.2
12	68.4 ± 0.1	106.8
15	63.9 ± 2.4	99.8
19	62.9 ± 3.5	98.3
23	70.8 ± 0.2	110.6
26	58.3 ± 6.9	91.1
29	70.8 ± 1.2	110.6
30	65.8 ± 1.5	102.8

Interdays (30 days)

Percentages remaining

Forced Degradation Studies

Physical stability
All solutions were initially clear and colourless and remained so for the duration of the study. Also, no visible particles were observed in any solution throughout the study period.

Action of UV light
Under UV light irradiation, the initial solution change to yellow at 24 h. Also the peak area diminished at 24 h, and then remain constant to at least 72 h.

Influence of temperature
Mixtures were heated in a water bath during 60 min at 40 ℃, 60 ℃, 80 ℃. No changes were significantly obtained in the chromatograms.

Influence of NaOH
Additions of different amounts of NaOH 0.1 M and 1 M to 500 µL of mixtures let to obtain a calibration graph with similar slopes compared to the sample in neutral medium. The higher difference observed in these chromatograms were the presence of diverse peaks corresponding to a degradation product (Rt: 2.3 min)

Influence of HCl

Additions of different amount of HCl 0.1 M and 1 M to 500 µL of mixtures let to obtain a calibration graph with similar slopes. The evolution of this peak with the time are showed in Figure 1(a,b) and Figure 2 (a,b)

HCl 0.1M

Figure 1 a): Rt: 1.32 min

Figure 1 b): Rt: 1.65 min

HCl 1M

Figure 2 a): Rt: 1.32 min

Figure 2 b): Rt: 1.65 min

Influence of H$_2$O$_2$

Additions of different amounts of H2O2 0.03% to 500 µL of mixtures let to obtain a calibration graph with similar slopes compared to the sample in neutral medium. Additions of H2O2 0.3% and 3% to the mixture showed an enhancement of the peak area and remain constant with the time. Figure 3 shows this effect.

Figure 3

Influence of NaClO

Additions of different amounts of NaClO 0.02 M to 500 µL of mixtures let to obtain a calibration graph with similar slopes compared to the sample in neutral medium. Additions of NaClO 0.2 M showed a diminution of the peak area at time 0 min respect the original signal but increased with the amount of NaClO added. With NaClO 2 M the peak area increased with respect to without NaClO, and then diminished at 20 min and remain constant with the time. (Figure 4)
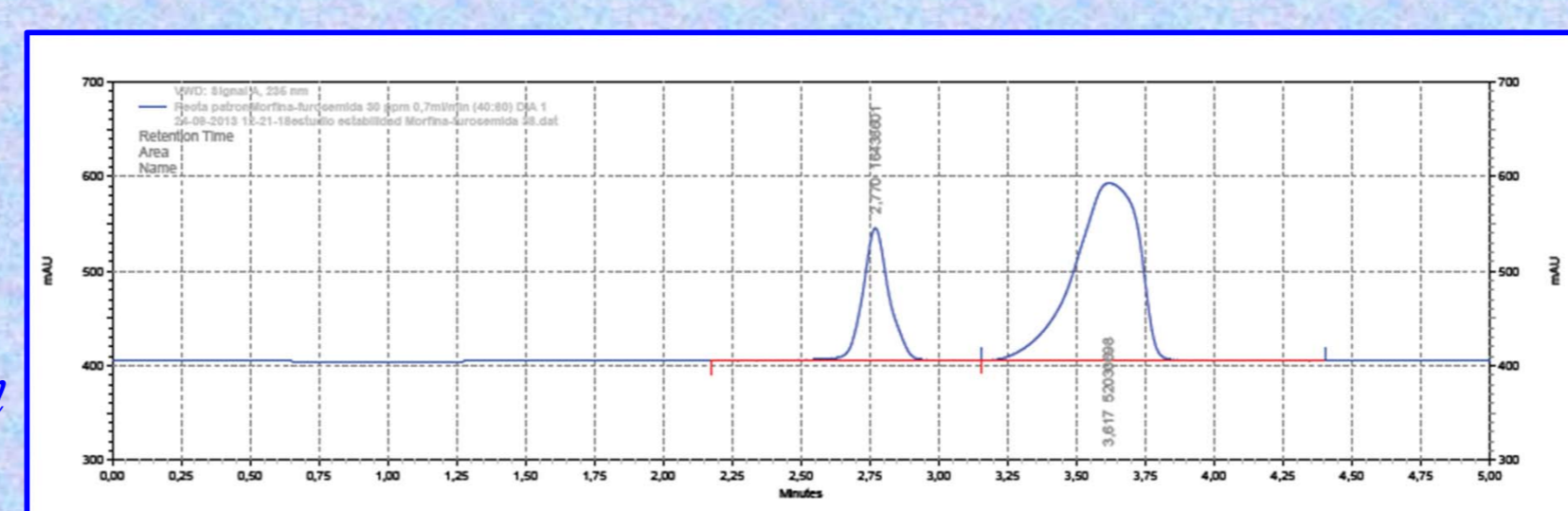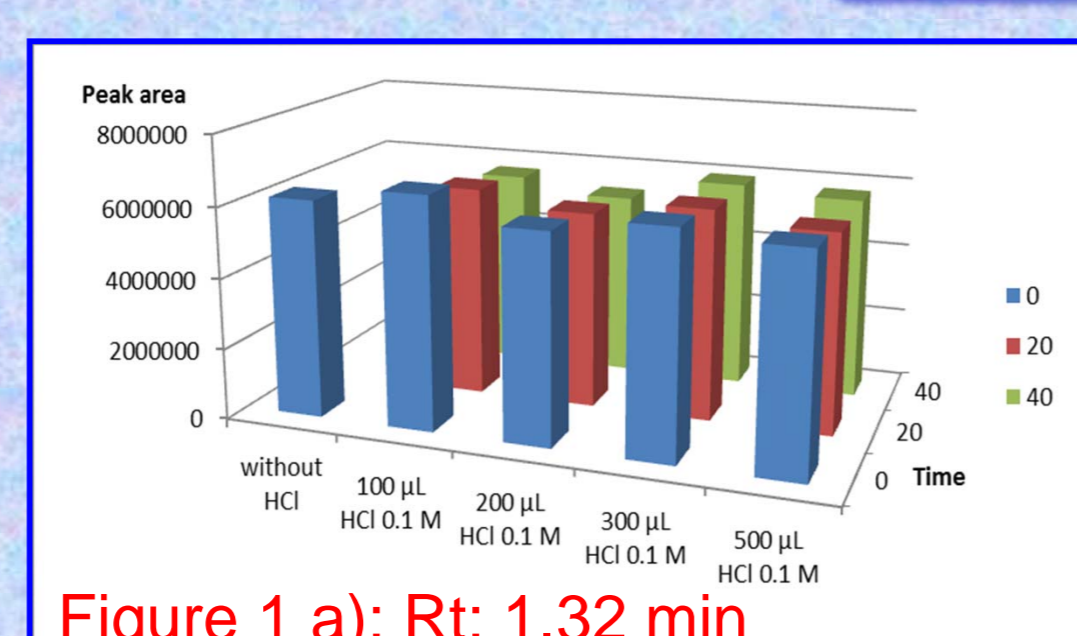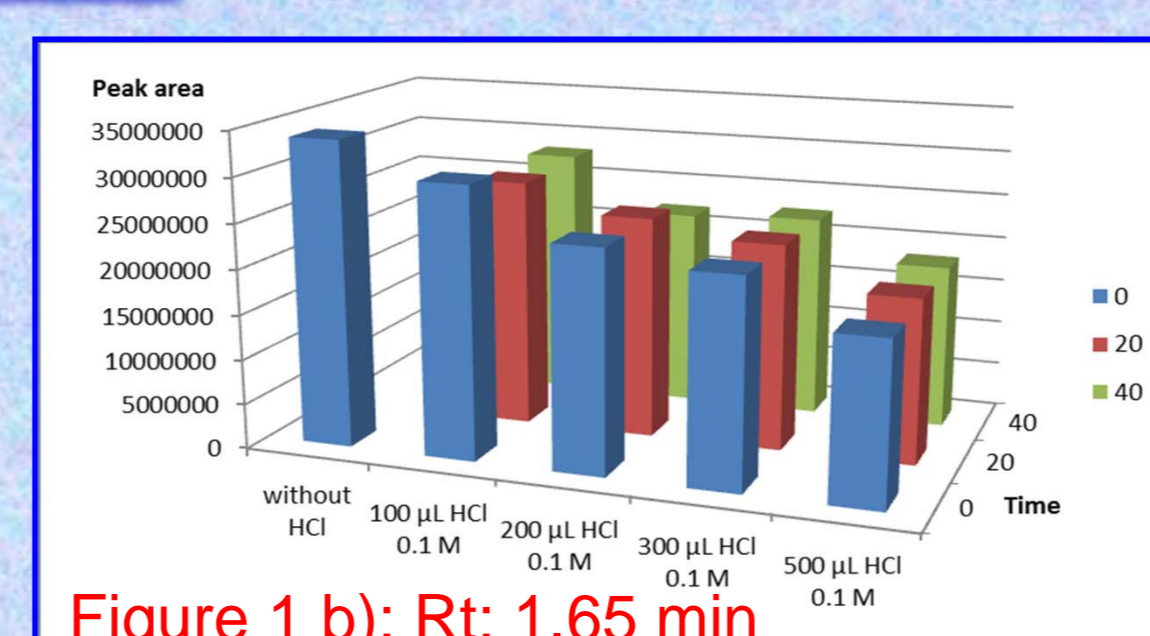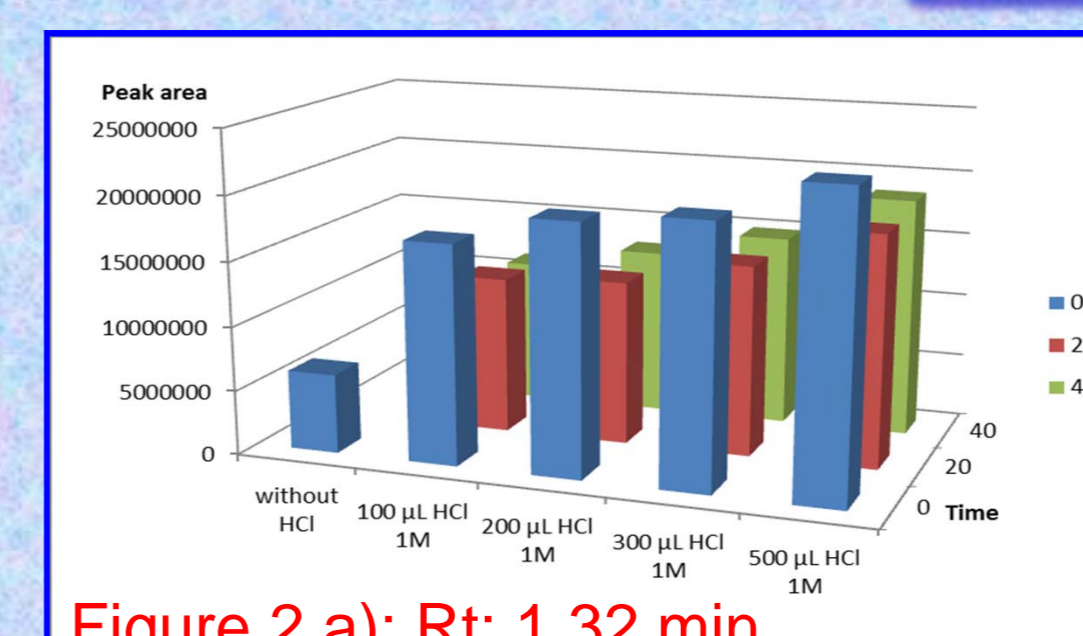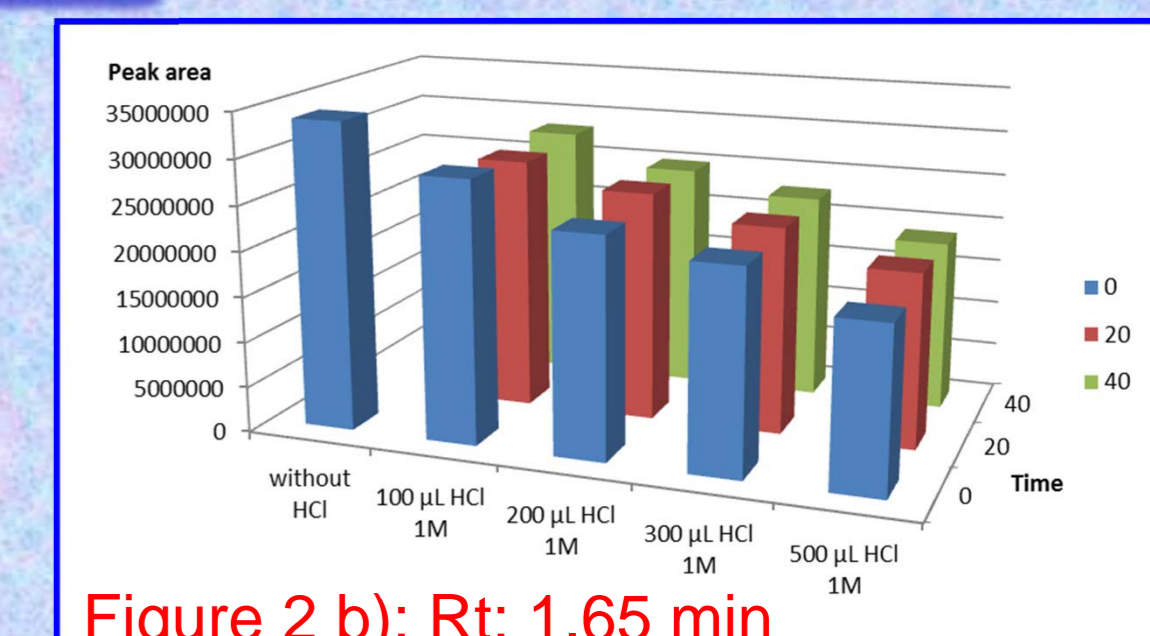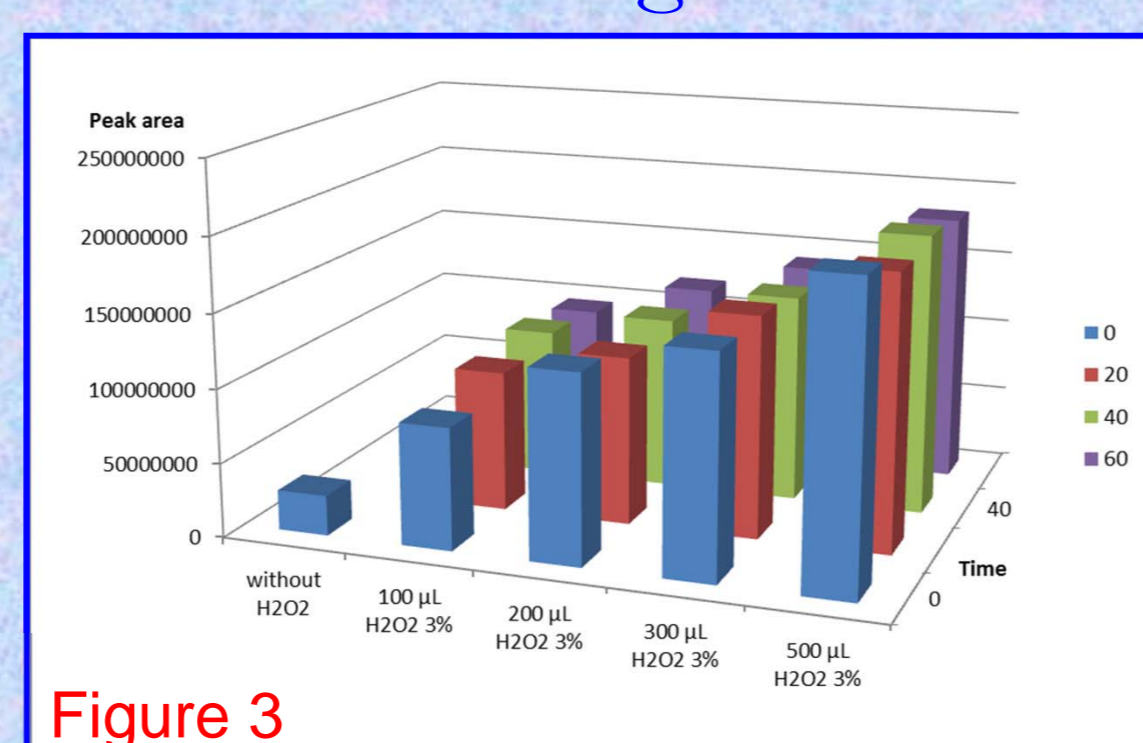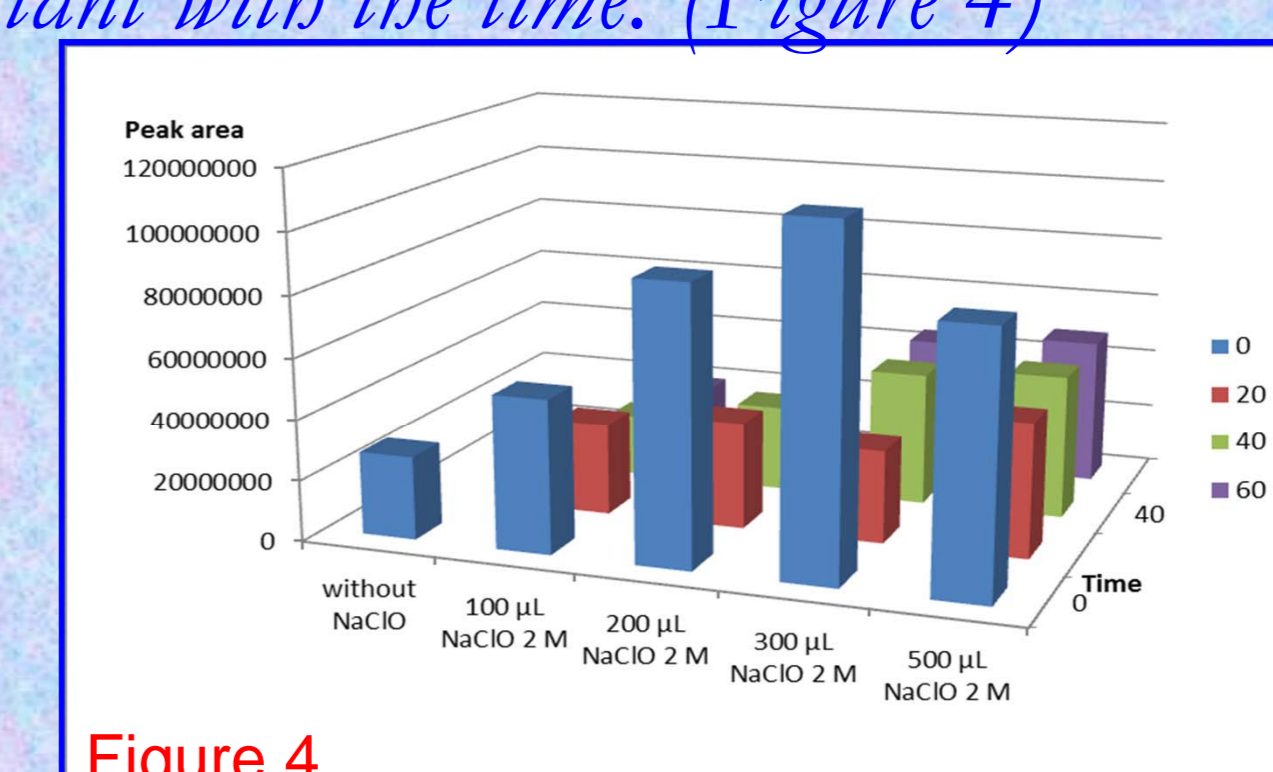

Figure 4

CONCLUSIONS

▸ Morphine and furosemide admixture diluted in NaCl 0.9% (concentration 1.0 and 0.6 mg/ml, respectively), is physically and chemically stable, in all studied conditions from at least 30 days.