

A Combined HPLC and LC-MS Approach for Evaluating Drug Stability in Elastomeric Devices: A Challenge for the Sustainability in Pharmacoeconomics

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Abstract

Objectives

A longer postoperative care, needed for patients admitted to the hospital, is expensive and associated with increased morbidity and mortality, when compared with the outpatient setting. Outpatient therapy with continuous infusion of drugs with elastomeric pumps represents an effective method to address this problem. The aim of this work is to analyse the benefits in using elastomeric devices and to test their behaviour towards drugs to changes during storage that could influence quality, safety and efficacy of the therapy.

Methods

Several drugs belonging to different therapeutic classes, including anticancer, analgesic opioids, local anesthetics and Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) have been studied using a combined HPLC/LC-MS approach. Each drug was loaded in three different brands of elastomeric devices and the samples were withdrawn over 7 days and submitted to HPLC/LC-MS analyses.

Key-Findings

All tested drugs showed high stability in each filled device, in fact only a low variability, less than 5 %, in term of percentage change in chromatographic areas, was observed. Moreover additional peaks, due to degradation of drug and/or to medical device-drug interaction, have not been detected both in HPLC and LC-MS analysis.

Conclusion

Thanks to the implementation, within clinical protocols, of the use of these infusion systems, two important goals can be achieved: a) the keeping of the quality of care also out of hospitals and b) the reduction of tangible costs as well as intangible costs in health care.

Keywords: Elastomers; Drug stability; Pharmacoeconomics; HPLC; LC-MS

Introduction

In clinical practise great number of drugs are used in long-term medical therapy such as analgesic opioids, Non-Steroidal Anti-Inflammatory Drugs (NSAIDs), anticancer drugs, antibiotics, local anesthetics.

A longer postoperative care, needed for patients admitted to the hospital, is expensive and associated with increased morbidity and mortality when compared with the outpatient setting. Outpatient therapy with continuous infusion of drugs, using elastomeric pumps represents an effective method to address this problem.

Elastomeric pumps are disposable devices for continuous infusion of a drug solution that consist of a balloon-tank made up of elastic material that exerts a constant pressure on the fluid in it which facilitate the movement of along its infusion line resulting in a constant established flow. Most modern pumps are characterized by accuracy of the flow, absence of latex, anti-crushing and anti-kinking infusion lines, lightness and easy handling [1].

An additional and attractive therapeutic advantage of elastomeric pumps is the control for self-administration of boluses a patient controlled administration in an economic and rapid way with brief information give to the patient. Additionally models, known as Multi-flow models, allow modifying the pre-set flow in according to clinical

needs [2]. The development of disposable nonelectric infusion pumps affords several advantages over traditional infusion systems. These advantages include ease of use, with no programming or troubleshooting, as well as the lack of the requisite power source [2,3].

Elastomeric pumps meet result in patient compliance adherence that is an important aspect that shouldn't be underestimated in comparison to other benefits. Indeed, during admission at the hospital either undergo surgery or to receive therapy, patients change their life style and sometimes the basic human rights (eating, mobility, privacy)

By using these infusion systems two important aspects could be reached:

- a) Improvement of the galenic formulation quality;

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b) Accurate pharmacoeconomic evaluation.

Patient morbidity and mortality have often resulted from incorrectly prepared or contaminated galenic products. In the preparation of these products, the use of closed-system and the aseptic transfer of sterile and non-pyrogenic pharmaceuticals (obtained by licensed manufacturers) into sterile final elastomeric containers, with the aid of a mechanical pump and appropriate sterile transfer tubing device, improve the quality of the final preparation, according to the quality assurance guidelines [4,5].

The acquisition and the use of elastomeric infusers could lead to a knocking down of costs in the therapy of postoperative hospital stay as well as of morbidity and mortality [6]. Reduction of the time spent by patients in the hospital represents a valid way to minimize costs, permitting a large number of patients who need more complicated treatment to find room to be accommodated in the busy oncologic units for instance and thus increase the quality and quantity of care with comparable resources. What is clearly evident is that general costs such as heating and acclimatization of hospital buildings, ordinary and extraordinary maintenance of the buildings, administrative and superstructure costs could be spread over and distributed across to a greater number of patients.

An additional aspect that should be considered in the evaluation of the use of elastomeric devices is their compatibility with the loaded drugs with respect to the drug pharmaceutical properties reported in technical sheets and their shelf lives. Moreover it must be considered the possibility that a concentration gradient, in time-dependent approach, may occur. In fact reactions between drugs and plastic materials (adsorption effects) could lead to immobilize the drug on the inner surface of infusion containers or infusion lines leading to a decrease in drug quantity administered to the patient. Moreover in the case of infusion of multiple drugs, the drug-drug interactions should be routinely investigated.

Thus, the evaluation of the drug stability of the most important classes of drugs administered thanks to these pumps could be defined a "milestone" for encouraging their use.

In this study, several drugs, belonging to four pharmaceutical classes (anticancers, analgesic opioids, local anesthetics and NSAIDs) in three different models of medical devices (brand undisclosed) have been evaluated. The drug stability for each drug in each medical device has been studied by combined HPLC/LC-MS method over a period of 7 days.

Materials and Methods

Drugs

The drug formulation was chosen considering the administration protocols currently used in clinical practise. C_0 indicated the concentration of the drug solution used to fill the pump and V indicated its volume.

Temperature of analysis

25 ± 0.5 °C

Medical device

Three of the most important suppliers in the development and marketing of these devices have provided the employed elastomeric pumps. The brands are not disclosed.

Filling procedure

Sample solutions of drugs (established volume V and concentration C_0), were transferred into the elastomeric pumps. C_0 and V of each drug are reported in Table 1. The filling procedure of the elastomeric pumps was executed according with protocols of the Unit of Antineoplastic Drug Handling (U.Ma.CA.) of the Cancer Institute "Giovanni Paolo II", Bari.

Preparation of test samples and sampling

T_0 sample was taken directly from the elastomeric pump (1 mL) immediately after filling (T_0), while the other samples were taken at established time intervals. 2 x 1mL samples were taken, because one sample was used for HPLC analysis and the other one for LC-MS determination. The samples were used as such or after dilution with NaCl 0.9% as reported in Table 2.

HPLC Apparatus

HPLC analyses were performed on an Agilent 1260 Infinity instrument equipped with 1260 DAD VL + detector controlled by OpenLAB CDS ChemStation Edition Software. The employed column was a C18 reverse phase Discovery® 25 cm x 4.6 mm, 5 µm. HPLC operating conditions (Wavelength, Flow, Mobile phase, Injection volume, Retention time, Column temperature) are reported for each drug in Table 2. All solvents were HPLC grade quality and all chemicals were purchased from Sigma-Aldrich Co. (St. Louis, USA).

LC/MS Apparatus

LC-MS analyses were performed on an Agilent 1100 LC/MSD trap system V spectrometer equipped with an electrospray ionization (ESI-MSⁿ) system. The samples (1 mL) were analysed after lyophilization and subsequent extraction with appropriate solvents.

Method Validations

Each HPLC method was validated by linear fit curve. Linearity is studied to determine the range over which analyte response is a linear function of concentration. In particular the regression line for each drug was obtained by preparing standard solutions at almost 10

| CLASS | DRUG | C_0 | V |
|--------------------------------|------------------------------|-----------|--------|
| Anticancer | 5-Fluorouracile | 25 mg/mL | 100 mL |
| Anticancer/ Immunomodulator | Methotrexate | 1mg/mL | 100mL |
| Anticancer | Mitoxantrone Dihydrochloride | 2 mg/mL | 9 mL |
| Anticancer | Vincristine Sulphate | 20 µg/mL | 50 mL |
| Anticancer | Vinblastine Sulphate | 1 mg/mL | 18 mL |
| Anticancer | Cytarabine | 5 mg/mL | 100 mL |
| Local Anesthetic | Ropivacaine Hydrochloride | 7.5 mg/mL | 50 mL |
| Local Anesthetic | Bupivacaine Hydrochloride | 10 mg/mL | 18 mL |
| Analgesic | Morphine Hydrochloride | 1 mg/mL | 40 mL |
| Analgesic | Oxycodone Hydrochloride | 3 mg/mL | 100 mL |
| FANS | Ketorolac Tromethamine | 1.8 mg/mL | 50 mL |
| Analgesic | Tramadol Hydrochloride | 5 mg/mL | 60 mL |

Table 1: Tested Drugs (filled solution: concentration C_0 and volume V).

| DRUG | Dil | (nm) | Flow | Mobile Phase | I.V. | RT | T _{Column} |
|------------------------------|----------|------|------------|---|--------|---------|---------------------|
| 5-Fluorouracile | 10 µg/mL | 278 | 1 mL/min | Water | 20 µL | 6 min | 25°C |
| Methotrexate | / | 284 | 1 mL/min | CH ₃ CN : NaH ₂ PO ₄ 30 mM (30:70) pH=3.5 | 20 µL | 3 min | 25°C |
| Mitoxantrone Dihydrochloride | / | 254 | 1mL/min | CH ₃ CN : NaH ₂ PO ₄ 30 mM (30:70) pH=3.5 | 2 µL | 3 min | 25°C |
| Vincristine Sulphate | / | 276 | 1mL/min | CH ₃ CN : NaH ₂ PO ₄ 30 mM (30:70) pH=3.5 | 100 µL | 8 min | 25°C |
| Vinblastine Sulphate | / | 276 | 1mL/min | MeOH : NaH ₂ PO ₄ 20 mM (30:70) pH=4.7 | 10 µL | 6 min | 25 °C |
| Cytarabine | 50 µg/mL | 284 | 1mL/min | CH ₃ CN: Water (20:80) | 20 µL | 3 min | 25°C |
| Ropivacaine Hydrochloride | 300µg/mL | 240 | 1mL/min | CH ₃ CN : NaH ₂ PO ₄ 30 mM (30:70) pH=3.5 | 20 µL | 4.5 min | 25°C |
| Bupivacaine Hydrochloride | / | 240 | 1mL/min | CH ₃ CN : NaH ₂ PO ₄ 30 mM (30:70) pH=3.5 | 10 µL | 6 min | 25°C |
| Morphine Hydrochloride | / | 210 | 1mL/min | CH ₃ CN : Tris 10 mM (10:90) pH=7.6 | 20 µL | 2.8 min | 25°C |
| Oxycodone Hydrochloride | / | 280 | 1.5 mL/min | CH ₃ CN: TRIS 10 mM (15:85); pH=7.6 | 20 µL | 13 min | 40°C |
| Ketorolac Tromethamine | / | 254 | 1mL/min | CH ₃ CN : NaH ₂ PO ₄ 30 mM (30:70) pH=3.5 | 20 µL | 16 min | 25 °C |
| Tramadol Hydrochloride | / | 274 | 1mL/min | CH ₃ CN : NaH ₂ PO ₄ 30 mM (30:70) pH=3.5 | 10 µL | 4 min | 25°C |

Table 2: HPLC Operating conditions: Dil (dilution factor); λ (wave length); I.V (Injection volume); RT (retention time); T (column temperature).

different concentrations and the analyses were performed in triplicate. The responses were measured as peak area and the calibration curves for each drug were obtained by plotting peak area against concentration.

Robustness

The precision of the method was verified by repeatability in a single day and the intermediate precision by different analysts on different days. Repeatability and intermediate precision were maintained by analysing the samples in triplicate. The results are summarized for each drug and the corresponding typical chromatograms have been reported. Moreover the critical parameters of flow rate and temperature were changed to assess the method performance.

Results

In this study the employed method involved the use of a combined HPLC-LCMS approach. Each drug was loaded in three different elastomeric devices. The samples of loaded solution were taken over the studied period and submitted to HPLC and LC-MS analyses allowing an unambiguous assessment of drug purity, stability and compatibility.

The used procedure for establishing purity and stability of each tested drug was to compare the area of peaks under interest with the one of a reference solution. In addition, the evaluation of the peak areas was used to appreciate the stability of drug concentration during the period of analysis. In fact, the compound could be chemically stable in accord to the producer's warnings, but inside the pump could be submitted to a gradient of concentration. Therefore the percentage changes of peak area were evaluated over 7 days. In particular % changes of areas, shown in the figures reported for each drug, were calculated according to the following formula:

$(T_0 - T_x / T_0) \times 100$, in which T_0 is the percentage of peak area corresponding to tested compound immediately subsequent to the filling of the elastomeric pump and T_x is the percentage area at different days. The T_0 is usually compared with the standard sample having the same concentration of filled solution. Final reported values of % change in peak areas correspond to the average value between three different determinations related to the three different elastomers. The acceptance

criterion in solution concentration are established by considering the clinical commonly used dose and the general criteria that the variation could be $\pm 5\%$.

5-Fluorouracile (5-FU)

It is one of the most common antineoplastic drugs used for colorectal cancer, stomach cancer, pancreatic cancer, breast cancer and cervical cancer [7-11]. The evaluated dose of 5-FU in the elastomeric pumps was 25 mg/mL. Table 3 displayed the % change in areas for 5-FU. The variation related to the peak at the third day corresponds to 1 mg/ml and then the variation could be considered safe for the patient, accordingly with the clinical protocols. The HPLC analysis (Figure 1) displayed good stability of 5-FU in the elastomeric devices and LC-MS confirmed no interaction between elastomer (ESI-/MS m/z: 130 ([M-H]⁻) and the drug.

Methotrexate

It is used to treat certain types of breast, skin, head and neck, and lung cancer. It is also used to treat severe psoriasis and rheumatoid arthritis. [12-14]. The evaluated dose of methotrexate in the elastomeric pumps was 1 mg/ml; the % changes in areas (<0.001mg/ml) were not significant according to the reference value and the use of Methotrexate in the tested devices can be considered adequate for a one week therapy (Table 4).

HPLC (Figure 2) and LC-MS analyses confirmed the stability of Methotrexate throughout the whole investigated period (ESI+/MS m/z: [M-2H⁺+Na]⁺).

Mitoxantrone

It is used for treating acute nonlymphocytic leukemia or advanced prostate cancer in certain patients [15,16]. The evaluated concentration was 2 mg/mL. The % changes in areas (Table 5) have been not significant (<0.26 mg/ml) and the use of mitoxantrone in the tested devices can be considered adequate for the therapy. HPLC (Figure 3) and LC-MS analyses confirmed the stability of the drug (ESI+/MS m/z: 445 ([M+H]⁺).

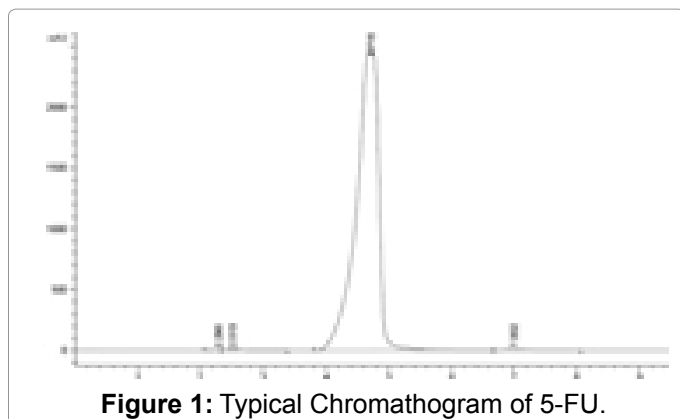


Figure 1: Typical Chromatogram of 5-FU.

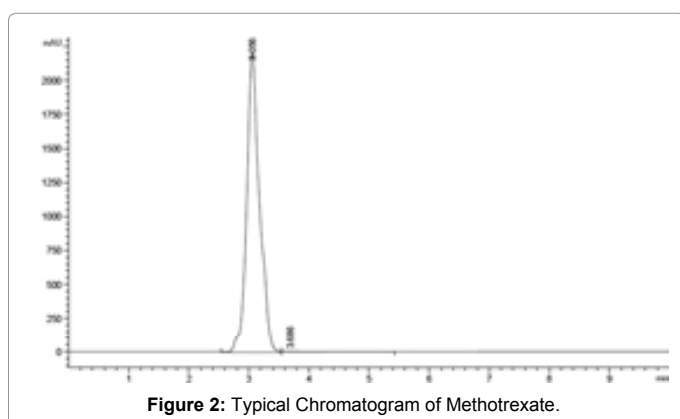


Figure 2: Typical Chromatogram of Methotrexate.

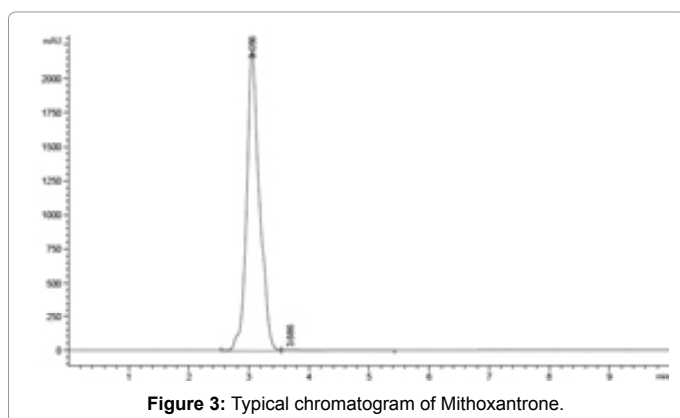


Figure 3: Typical chromatogram of Mithoxantrone.

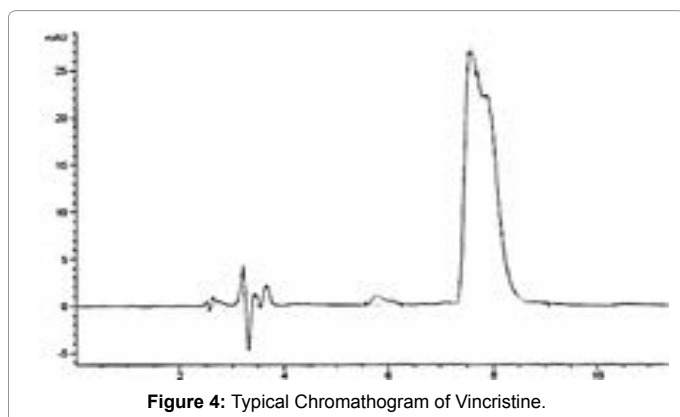


Figure 4: Typical Chromatogram of Vincristine.

Vincristine

It is used for treating certain types of cancer (leukemia, Hodgkin disease, non-Hodgkin lymphomas, rhabdomyosarcoma, neuroblastoma) [17-19]. The concentration of filled solution was 20 $\mu\text{g}/\text{mL}$. Vincristine displayed little variations in % changes in areas. In particular the % changes (Table 6) were less than 0.98 % and this finding is compatible with the common dosage used in therapy. HPLC (Figure 4) and LC-MS analyses confirmed the stability of Vincristine and no interactions with the devices have been observed ($\text{ESI}^+/\text{MS m/z}$: 847 ($[\text{M}+\text{Na}]^+$).

Vinblastine

It is an antineoplastic agent used in treating different tumours such as Breast Cancer, testicular cancer, bladder cancer and Hodgkin's Disease [17,20]. The tested concentration was 1 mg/mL . The % changes in areas have been < 1.28 mg/ml (Table 7). By considering the common dosage of vinblastine and the administration protocols the use of Vinblastine in the tested devices can be considered adequate for the therapy. HPLC (Figure 5) and LC-MS analyses confirmed the stability of Vinblastine and no interactions with the devices have been observed ($\text{ESI}^+/\text{MS m/z}$: 812 ($[\text{M}+\text{H}]^+$).

Cytarabine

It is an antimetabolite and is used for the treatment of several cancers such as Acute Nonlymphocytic Leukemia, non-Hodgkin's Lymphoma, Chronic Myelogenous Leukemia, Acute Myeloid Leukemia, Leukemia, Meningeal Leukemia [21]. The evaluated concentration in this work was 5 mg/mL . Considering the common dosage of Cytarabine and the administration protocols its use in the tested devices can be considered adequate for the therapy (Table 8). HPLC (Figure 6) and LC-MS analyses confirmed the stability of Cytarabine and no interactions with the devices have been observed ($\text{ESI}^+/\text{MS m/z}$: 243 ($[\text{M}+\text{Na}]^+$). In the chromatogram two unsolved peaks are present. This aspect has been investigated and the results confirmed these peaks belong to the same drug and they are due to ion pairs in the reported experimental conditions.

Ropivacaine

It is used for inducing loss of perception during surgical procedures or for short-term pain management [22-24]. The evaluated concentration was 7.5 mg/mL . Ropivacaine in the tested elastomeric pumps didn't display wide variations in % change of areas and the drug could be employed in therapy using these systems (Table 9).

HPLC (Figure 7) and LC-MS analyses confirmed the stability of Ropivacaine and no interactions with the devices have been observed ($\text{ESI}^+/\text{MS m/z}$: 275 ($[\text{M}+\text{H}]^+$).

Bupivacaine

It is used for inducing spinal anesthesia for certain medical or surgical procedures [25,26]. The evaluated concentration was 10 mg/mL . Bupivacaine in the tested elastomeric pumps didn't display wide variations in % change of areas and also this drug could be employed in therapy using these systems (Table 10). HPLC analysis and LC-MS analyses confirmed the stability of Bupivacaine and no interactions with the devices have been observed ($\text{ESI}^+/\text{MS m/z}$: 289 ($[\text{M}+\text{H}]^+$).

Morphine

It is used to treat moderate to severe pain. The filled solution had a concentration of 1 mg/mL . Morphine displayed only a little variation

| 5-Fluorouracile | | |
|-----------------|----------------|-----------------------------|
| Days | AREA (average) | % Change In Areas (average) |
| 0 | 94.77 | 0,00 |
| 1 | 96.70 | 2,04 |
| 2 | 97.87 | 3,27 |
| 3 | 98.66 | 4,10 |
| 4 | 96.98 | 2,33 |
| 7 | 97.17 | 2,53 |

Table 3: % Change in Areas for 5FU.

| Methotrexate | | |
|--------------|----------------|-----------------------------|
| Days | AREA (average) | % Change In Areas (average) |
| 0 | 99,99 | 0,00 |
| 1 | 99,99 | 0,00 |
| 2 | 99,99 | 0,00 |
| 3 | 99,99 | 0,00 |
| 4 | 99,99 | 0,00 |
| 7 | 99,67 | 0,32 |

Table 4: % Change in Areas for Methotrexate.

| Mitoxantrone | | |
|--------------|----------------|-----------------------------|
| Days | AREA (average) | % Change In Areas (average) |
| 0 | 99,76 | 0,00 |
| 1 | 99,77 | 0,01 |
| 2 | 99,66 | 0,10 |
| 3 | 99,87 | 0,11 |
| 4 | 99,89 | 0,13 |
| 7 | 99,87 | 0,11 |

Table 5: % Change in Areas for Mitoxantrone.

| Vincristine | | |
|-------------|----------------|-----------------------------|
| Days | AREA (average) | % Change In Areas (average) |
| 0 | 97,00 | 0,00 |
| 1 | 97,17 | 0,17 |
| 2 | 97,98 | 0,98 |
| 3 | 97,98 | 0,98 |
| 4 | 97,17 | 0,17 |
| 7 | 97,98 | 0,98 |

Table 6: % Change in Areas for Vincristine.

| Vinblastine | | |
|-------------|----------------|-----------------------------|
| Days | AREA (average) | % Change In Areas (average) |
| 0 | 99,04 | 0,00 |
| 1 | 95,90 | 2,18 |
| 2 | 96,50 | 1,57 |
| 3 | 96,35 | 1,72 |
| 4 | 96,49 | 1,58 |
| 7 | 97,15 | 0,90 |

Table 7: % Change in Areas for Vinblastine.

in % change of areas (<0.052 mg/ mL) and the drug could be employed in therapy using these systems (Table 11) [26-29]. Moreover the drug showed high stability in each filled device as confirmed by HPLC (Figure 9) and LC-MS analyses (ESI⁺/MS m/z: 286 ([M+H]⁺)).

Oxycodone

It is an opioid used in pain medication [30,31]. The evaluated concentration was 3 mg/mL. The % changes in areas have been not significant (<0.051 mg/ml) and the use of Oxycodone in the tested devices can be considered adequate for the therapy (Table 12). Moreover the drug showed high stability in each filled device as

confirmed by HPLC (Figure 10) and LC-MS analyses (ESI⁺/MS m/z: 316 ([M+H]⁺). In the chromatogram two unsolved peaks are present. This aspect has been investigated and the results confirmed these peaks belong to the same drug and they are due to ion pairs formed in the reported experimental conditions.

Ketorolac

It is a nonsteroidal anti-inflammatory drug [32]. The evaluated concentration was 1.8 mg/mL. The % changes in areas have been not significant and the use of Ketorolac in the tested devices can be considered adequate for the therapy (Table 13). Moreover the drug showed high stability in each filled device as confirmed by HPLC (Figure 11) and LC-MS analyses (ESI/MS m/z: 254 ([M-H]⁻)). In the chromatogram two unsolved peaks are present and further investigations. Confirmed these peaks belong to the same drug and are due to ion pairs formed in the reported experimental conditions.

Tramadol

It is a narcotic-like pain reliever [33]. The evaluated concentration was 5 mg/mL. The % changes in areas have been not significant and the use of Tramadol in the tested devices can be considered adequate for the therapy (Table 14). Moreover the drug showed high stability in each filled device as confirmed by HPLC (Figure 12) and LC-MS analyses (ESI⁺/MS m/z: 264 ([M+H]⁺). In the chromatogram two unsolved peaks are present and further investigations. Confirmed these peaks belong to the same drug and are due to ion pairs formed in the reported experimental conditions.

Discussion

Most of the studied drugs didn't display large variations in % change of areas. In particular the % variability for all elastomers is less than 2% excepting for 5-FU that displayed 4% after 3 days. However, this variation is acceptable taking into account the therapeutic window of the drug. Moreover, all tested drugs showed high stability in each filled device as confirmed by HPLC and LC-MS analyses. The findings suggest that it is advisable they can be used for administering antineoplastic agents, for long-term therapy and post-operative treatments.

Long-term anesthetics are used in the treatment of acute pain of peripheral nerve blocks to achieve in post-traumatic pain. Relying on the obtained results Ropivacaine and Bupivacaine can be administered with the elastomeric device and they result good candidates ambulatory use.

In pain therapy one of the most important parameters to control

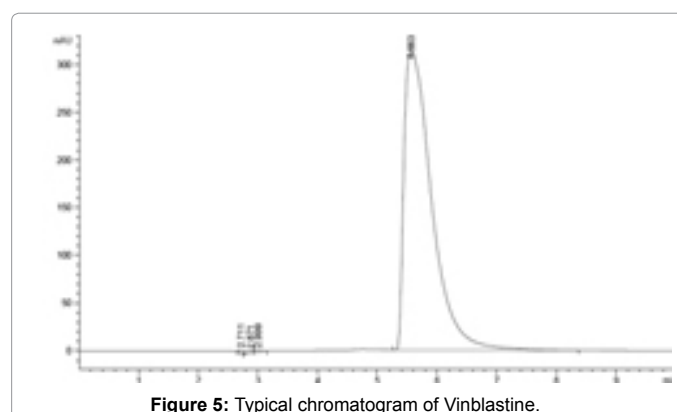
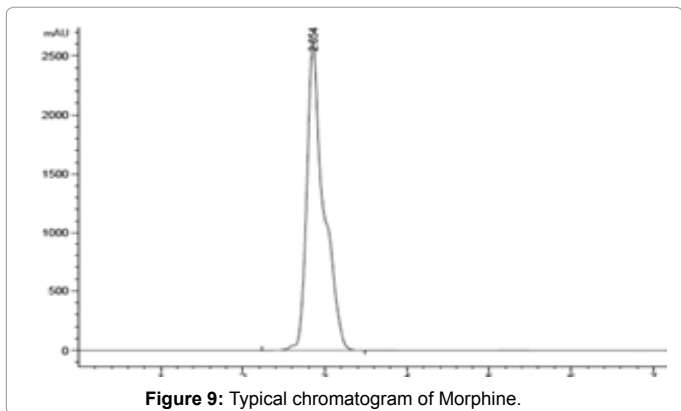
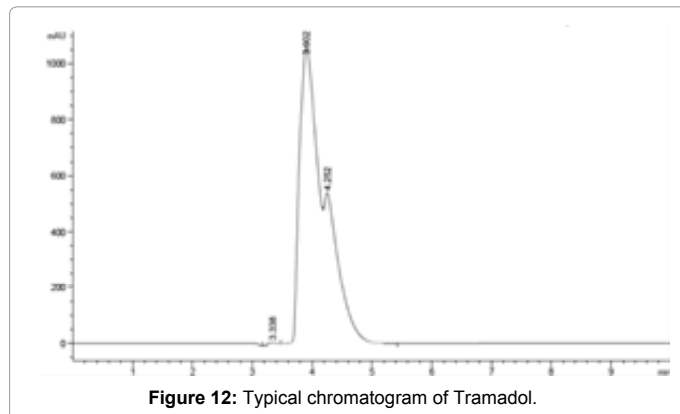
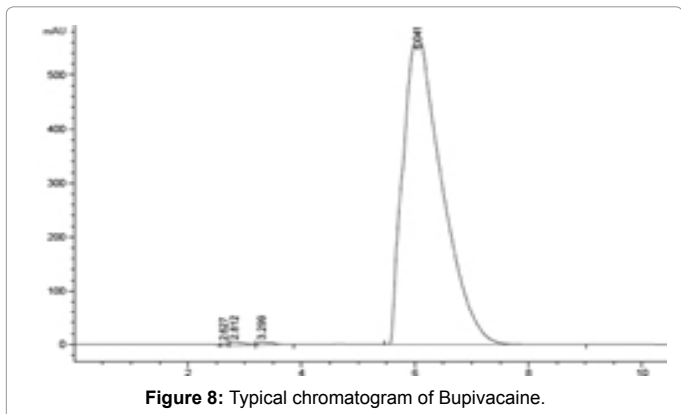
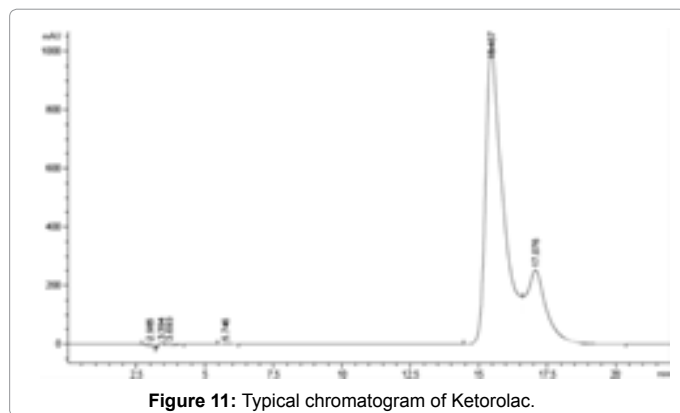
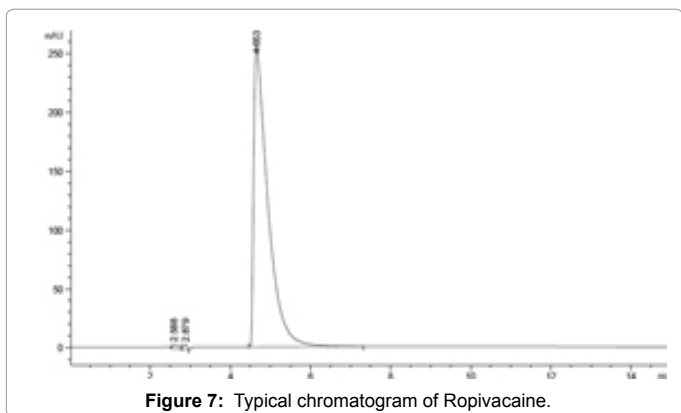
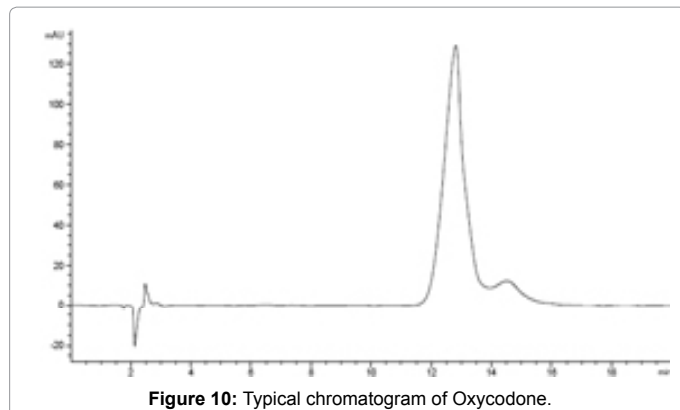
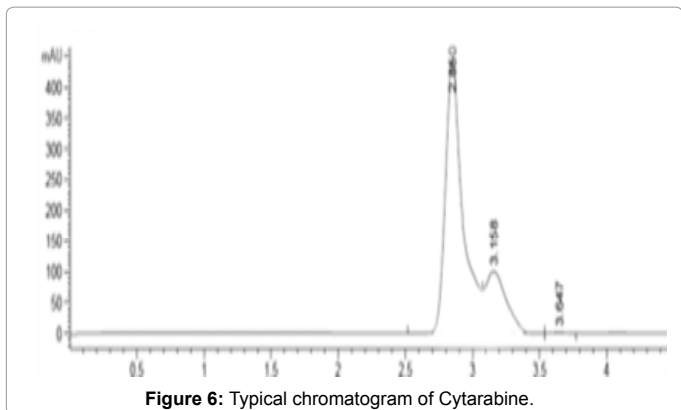


Figure 5: Typical chromatogram of Vinblastine.



| Cytarabine | | |
|------------|----------------|-----------------------------|
| Days | AREA (average) | % Change In Areas (average) |
| 0 | 99,68 | 0,00 |
| 1 | 99,39 | 0,29 |
| 2 | 98,53 | 1,15 |
| 3 | 97,98 | 1,70 |
| 4 | 98,43 | 1,25 |
| 7 | 97,91 | 1,77 |

Table 8: % Change in Areas for Cytarabine.

| Ropivacaine | | |
|-------------|----------------|-----------------------------|
| Days | AREA (average) | % Change In Areas (average) |
| 0 | 99,99 | 0,00 |
| 1 | 99,98 | 0,01 |
| 2 | 99,98 | 0,01 |
| 3 | 99,97 | 0,02 |
| 4 | 99,97 | 0,02 |
| 7 | 99,97 | 0,02 |

Table 9: % Change in Areas for Ropivacaine.

| Bupivacaine | | |
|-------------|----------------|-----------------------------|
| Days | AREA (average) | % Change In Areas (average) |
| 0 | 99,13 | 0,00 |
| 1 | 99,13 | 0,00 |
| 2 | 99,58 | 0,45 |
| 3 | 99,31 | 0,18 |
| 4 | 99,30 | 0,17 |
| 7 | 99,22 | 0,09 |

Table 10: % Change in Areas for Bupivacaine.

| Morphine | | |
|----------|----------------|-----------------------------|
| Days | AREA (average) | % Change In Areas (average) |
| 0 | 100 | 0,00 |
| 1 | 99,98 | 0,02 |
| 2 | 99,74 | 0,26 |
| 3 | 99,55 | 0,45 |
| 4 | 99,49 | 0,51 |
| 7 | 99,48 | 0,52 |

Table 11: % Change in Areas for Morphine.

| Oxycodone | | |
|-----------|----------------|-----------------------------|
| Days | AREA (average) | % Change In Areas (average) |
| 0 | 100 | 0,00 |
| 1 | 100 | 0,00 |
| 2 | 100 | 0,00 |
| 3 | 100 | 0,00 |
| 4 | 100 | 0,00 |
| 7 | 99,83 | 0,17 |

Table 12: % Change in Areas for Oxycodone.

| Ketorolac | | |
|-----------|----------------|-----------------------------|
| Days | AREA (average) | % Change In Areas (average) |
| 0 | 98.97 | - |
| 1 | 98.71 | 0.26 |
| 2 | 98.39 | 0.59 |
| 3 | 97.93 | 1.05 |
| 4 | 98.18 | 0.79 |
| 7 | 98.78 | 0.19 |

Table 13: % Change in Areas for Ketorolac.

| Tramadol | | |
|----------|---------------|-----------------------------|
| Days | AREA(average) | % Change In Areas (average) |
| 0 | 99.58 | - |
| 1 | 99.57 | 0.01 |
| 2 | 99.44 | 0.14 |
| 3 | 99.89 | 0.31 |
| 4 | 99.43 | 0.15 |
| 7 | 99.52 | 0.06 |

Table 14: % Change in Areas for Tramadol.

is the constant blood concentration of an analgesic opioid, so the use of elastomeric pumps in this field could allow the achievement of this goal. Also analgesic opioids such as Morphine and Oxycodone are suitable to be used with elastomeric devices because chemical and physical stability and compatibility have been demonstrated.

Non-opioid drugs employed in pain therapy such as Ketorolac and Tramadol displayed high stability and compatibility and the results candidate them for their use in ambulatory therapy.

Conclusion

Currently, an emerging social issue is to optimize resources in the health sector. Hence the necessities to concentrate health care costs and think about the use of innovative and sustainable systems for effective therapies. The employ of elastomeric pumps in normal clinical protocols could reduce tangible costs as well as intangible costs in health care. Ambulatory pumps may reduce the cost of the staff and other costs due to work capacity reduction, loss of earnings, loss of productivity, loss of leisure time for patients, cost of the trip to the hospital. This would include not just the patient themselves but also their family and society as a whole.

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