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(REVIEW ARTICLE)

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Compatibility and stability of drug mixtures: An overview

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Abstract

The use of the subcutaneous route for the administration of medications in Palliative Care (PC) is a very interesting route when the oral route is not available. The use of infusers for continuous infusion allows the control of symptoms in a simple way. In many cases it is necessary to administer more than one drug, so mixing them in the same infuser is the best alternative. However, there are few published data on the stability of mixtures, and even less if we focus on data on the physicochemical stability of drug mixtures in infuser-type delivery systems and stored in conditions of temperature and light similar to those of practice assistance. The objective of this review is to analyze the available evidence on the stability of the mixtures identified through bibliographic review in tertiary sources (Technical file, book Trissel's Stability of Compounded Formulation, Micromedex, stabilis.org, pallcare.info and palliativedrugs.com). This consultation is completed with a bibliographic search in the main biomedical databases: EMBASE and Pub Med and with a review of the primary sources of interest resulting from the previous search.

Keywords: Palliative care; Drug mixture; Compatibility; Stability; Infuser

1. Introduction

The aging of the population and the growing number of people with chronic degenerative diseases and cancer represent a major challenge for health services worldwide and pre-eminently in developed societies. Many of these patients, at the end of their life, suffer intense suffering and require health and social care that involves all areas of care.

The Palliative Care (PC) movement started in the UK during the 1970s (Hospice Movement) and spread internationally. At this time, Cicely Saunders was the first healthcare provider to guide her professional work towards the search for specific solutions for the requirements of patients with terminal illness, which gave rise to the philosophy and principles that are known today as PC. Saunders founded St. Christopher's Hospice, which can be considered the cradle of the modern Hospice Movement and PCs.

The World Health Organization (WHO) defines PC as "the approach that improves the quality of life of patients and families who face the problems associated with life-threatening diseases, through the prevention and alleviation of suffering, through the early identification and impeccable evaluation and treatment of pain and other physical, psychosocial and spiritual problems". This conception of PC recognizes that people with diseases other than cancer, which are irreversible, progressive and with a terminal phase, can also benefit from its application.

Patients in the end of life may present with multiple symptoms, depending on the nature and stage of their disease. In the case of cancer patients, the location of the tumour, its grade, local extension and metastasis determine the symptoms.

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National studies on the prevalence of symptoms refer mainly to cancer patients. In these series, pain, asthenia and anorexia appear in more than 70% of the patients.

The use of drugs to control symptoms in PC has some special characteristics that must be considered. Patients with advanced or terminal illness constitute a particularly vulnerable population. Your environment and the different psychological factors can have a great influence on your physical well-being and on your response to drug treatment, a response that will sometimes be unpredictable.

These patients are often elderly, frail or with multi-organ involvement and poly-medicated, with the consequent risk of interactions and pathogenesis.

The challenge for professionals and caregivers is to treat symptoms effectively, maintaining maximum patient comfort and minimizing adverse effects and inconveniences of treatment or very complex guidelines.

The choice of the route of administration depends on factors related to the patient, the drug and organizational factors (availability of formulations, human resources, etc.).

The main route of administration in PC is oral, since it is a simple, non-invasive and acceptable route for most patients.

However, there are situations in which oral administration of drugs is not possible (for example, when the patient has nausea and vomiting, seizures, dysphagia or intestinal obstruction).

In cases where oral drug administration is not possible, alternative routes of administration need to be used. Examples of these alternative routes are the intravenous route, the intramuscular route, the rectal route, the transdermal route, the sublingual route or the subcutaneous route.

At present, the subcutaneous route is considered the most appropriate of the alternative routes, especially at the community level in order to maintain the patient's autonomy and be able to live their last days in their natural environment.

The subcutaneous route is not very aggressive and allows self-administration by the patient or by the patient’s family.

In many cases it is necessary to administer more than one drug, so mixing them in the same infuser would be the best alternative. However, there are few published data on the stability of mixtures, and even less if we focus on data on the physical-chemical stability of mixtures in infuser-type systems and preserved in conditions of temperature and light similar to those of healthcare practice.

For these reasons this review is focused into stabilities studies of drug mixtures stored into infuser used in PC.

A query is made on the stability of these drugs and drug mixtures in tertiary sources (Technical file, Trissel's Stability of Compounded Formulation book, Micromedex, stabilis.org, pallcare.info and palliativedrugs.com). This query is completed with a bibliographic search in the main biomedical databases: EMBASE and PubMed. (Search strategy (“Drug stability” [MeSH] OR “Drug Incompatibility” [MeSH]) AND XXX AND XXX) where XXX corresponds to each of the active principles of the mixture of interest.

The localized articles are peer-reviewed and those that meet the selection criteria are selected:

1.1. Inclusion criteria

- Articles in Spanish or English.
- Articles on physical and / or chemical compatibility of drug mixtures.

1.2. Exclusion criteria

- Impossibility of locating the full text.
- Articles about drugs for which no information has been requested.

2. Bibliographic search

The bibliographic search was carried out in 9 databases: AEMPS online drug information centre, Pallcare, Palliative Drugs, Embase, Medline, Gerión, Google, Micromedex and Stabilis.

Information on bibliographic references that meet all the inclusion criteria and none of the exclusion criteria is included in the study.

Other articles were excluded. The reason for exclusion was:

- Impossibility of obtaining full text
- Article in a language other than English or Spanish
- Active ingredient not marketed in Spain
- Objective of the study not related to stability or compatibility
- Administration method other than the one studied
- Duplicates

Some countries such as the United Kingdom or Ireland have carried out national surveys to identify the drug mixtures frequently used in continuous subcutaneous infusion [1-5]. These studies, except the last one, are old and do not reflect current practice. In the study by Dickman et al., which is very recent, a survey is carried out among pharmacists related to PC on the mixtures prepared in their services during the last 12 months and complemented with a Delphy study with 15 health professionals with the objective of identifying the five most used drug mixtures for the control of complex or refractory symptoms. It concludes that the most frequent mixtures contain three drugs.

In general, studies on the identification of mixtures for continuous subcutaneous infusion conclude that there is little data on stability and compatibility for the most frequently used mixtures. This is because laboratory tests are expensive and time consuming and the number of potential combinations is immense.

Despite the expansion of the practice of PCs, even today we have little information on the stability and compatibility of mixtures that can be used. This comes from bibliographic sources that compile information in many cases based solely on the visual compatibility of the mixtures. Some mixtures may appear physically compatible in the absence of changes in turbidity or colour or the appearance of precipitate, but the risk of chemical incompatibility cannot be ruled out. Furthermore, most of the studies are carried out in infusion bags or syringes, while in our case the objective is to condition them in an elastomeric infuser, which exerts high pressure on the solution and which could act as an accelerator of instability reactions.

There is therefore clearly a need to identify the stability and compatibility of drug mixtures used in PC patients.

The information obtained through the different databases used is collected in table 1.

Table 1 Described the main results of the included studies, in chronological order

Comments	Ref
Physical compatibility study (visual inspection) of cytostatic drugs mixed with support drugs (droperidol, metoclopramide, furosemide, heparin) simulating the administration in Y.	6
Visual stability study of binary mixtures of midazolam at 25°C for up to 4 hours with various drugs: Mixtures with dimenhydrinate, pentobarbital, perphenazine, prochlorperazine, and ranitidine are unstable.	7
Chemical stability study by HPLC of binary morphine mixtures (with dexamethasone, metoclopramide or haloperidol) for 7 days at room temperature. The mixtures are indicated to be stable, but no further data on methodology or results are given. In addition, a clinical study is detailed in which these mixtures are administered to 117 patients with good efficacy and safety.	8
Physical compatibility study (visual inspection) of morphine (sulphate) and meperidine with other drugs simulating the administration in Y for 4 hours. The compatibility of 21 drugs with morphine and 28 drugs with meperidine, diluted in glucose serum, was tested.	9

Chemical stability study by HPLC of the mixture of morphine hydrochloride + scopolamine diluted in water for injection, stored at room temperature and 37°C was carried out by Lawson et al. Only scopolamine concentrations are determined. The mixture is apparently stable.	10
Chemical stability study of the morphine - midazolam mixture in PVC containers to determine its shelf life. Solutions were prepared at different concentrations in physiological serum and 5% glucose. The pH and the concentration of the active ingredients were determined by HPLC. Morphine presents concentrations lower than 90% of its initial concentration from the second day, for which the authors consider that the mixture is unstable under the conditions tested.	11
Physical stability study (visual inspection, pH) and chemical (HPLC) of mixtures of hydromorphone with seven other drugs (ampicillin, cefazolin, ceftazidime, cloxacillin, diazepam, phenytoin and phenobarbital) for 24 hours at room temperature. The only compatible mixture is hydromorphone + ceftazidime, in the others the degradation of one or both components is observed.	12
Physical stability study (visual inspection, osmolality) of morphine-metoclopramide and morphine-metoclopramide-haloperidol mixtures stored at 25 ° C for 7 days. Haloperidol reduces the stability of the mixture, especially when used at high concentration.	13
Physical stability study (visual inspection, pH) and chemical (HPLC, determination of hyaluronidase activity by adding hyaluronic acid) of mixtures of both drugs at various concentrations for 7 days at 4, 23 and 37°C. The mixture is physically stable and the hydromorphone concentration does not decrease, however the hyaluronidase activity decreases considerably during storage, so the authors recommend not mixing them.	14
Physical stability study (visual inspection, turbidity) and chemical (HPLC) of binary mixtures of ondansetron + morphine sulphate and ondansetron + hydromorphone at various concentrations, diluted in physiological serum and stored at 4, 22 and 32°C. The mixtures are stable for at least 7 days at 32°C and at least 31 days at 4 and 22°C.	15
Study of physical stability (visual inspection, pH) and chemical (HPLC) of ternary mixtures of bupivacaine + morphine + clonidine in bags for 90 days were carried out by Wulf et al. The mixture is compatible.	16
Physical stability study (visual inspection) and chemical (HPLC) of mixtures of morphine sulphate + midazolam or morphine sulphate + haloperidol, diluted in physiological or glucose serum and stored for 14 days at room temperature. The morphine + midazolam mixture is stable but the morphine + haloperidol mixture precipitates upon mixing.	17
Observational study in patients using subcutaneous infusion to determine the incidence of skin reactions and clinical efficacy. The results are not included in the subsequent analysis due this work does not carry out a physical or chemical compatibility study on any specific mixture. Skin reactions may be due to reasons other than the instability of the mixture.	18
Physical stability study (visual inspection) of drug mixtures with midazolam simulating Y administration. The drugs were diluted in 5% glucose serum, except for ampicillin, which was diluted in physiological serum. The determined stability time (approx. 4 hours), it is considered insufficient to extrapolate the results for ICSC, therefore the results are not included in the subsequent analysis except for the documentation of incompatibility.	19
Observational study in palliative patients administered octreotide in ICSC by syringe infuser, alone or in combination with other medications. Good tolerance and compatibility are observed with no signs of precipitation with the naked eye for 48 hours at room temperature.	20
Study of physical stability (loss of volume, pH, visual observation) and chemical (HPLC) of a mixture of morphine sulphate + metoclopramide in infuser, syringe and bag, diluted in saline or glucose, stored at 4 and 22°C protected from light. Morphine remains stable but metoclopramide degrades with time, especially if the diluent is glucose serum, and the conditioning is in an infuser. The authors recommend using the mixture for a maximum of 14 days if stored at 22°C and 4 months if stored refrigerated, using saline for dilution. It is important to highlight that the morphine used in this study is the sulphate salt, while the parenteral morphine that we have in Spain is the hydrochloride salt.	21
Study of the physical stability (visual observation and turbidimetry) of a mixture of an opioid (fentanyl, hydromorphone, methadone and morphine) with other drugs (atropine, dexamethasone, diazepam, diphenhydramine, haloperidol, hydroxyzine, ketorolac, Lorazepam, methotrimeprazine, midazolamide,	22

phenobarbital, phenytoin, scopolamine), in physiological serum packed in a PVC bag and stored at room temperature (approximately 22°C) under constant fluorescent light for 48 hours. All mixtures except that containing phenytoin are physically stable.	
Description of an HPLC technique to measure the stability of mixtures of ondansetron with various drugs in physiological serum. It does not provide details on the stability of these mixtures since it focuses on the description of the methodology used.	23
Physical stability study simulating administration in Y by visual inspection of drugs commonly used in intensive care for 4 hours. Since the study time is less than that considered for ICSC, the results are not included in the subsequent analysis except for evidence of incompatibility.	24
Study of physical stability (visual inspection) and chemical (HPLC) of two mixtures in physiological serum until a volume of 10 ml is obtained: - Morphine tartrate 400 mg + droperidol 2 mg + dexamethasone 8 mg + butyl scopolamine 20 mg + midazolam 8 mg - Morphine tartrate 40 mg + droperidol 2 mg + dexamethasone 8 mg + butyl scopolamine 20 mg + midazolam 5 mg The mixtures were stored protected from light, at 21-23 or 4-8°C for two weeks. Refrigerated mixtures are stable throughout the study period. The mixtures at room temperature maintain> 90% of the initial content for 12 days in the case of the first mixture and for 5 days the second, midazolam being the active principle that degrades first.	25
Compatibility study of granisetron with 91 drugs in glucose or physiological serum by visual inspection and turbidimetry for 4 hours to simulate the administration in Y.	26
Physical stability study (visual inspection, pH) and chemical (HPLC) of ternary mixtures of fentanyl + midazolam + butylscopolamine or fentanyl + midazolam + metoclopramide, in polypropylene syringe, stored for 10 days at 32°C protected from light. The mixtures are stable for at least 7 days.	27
Study of physical stability (visual observation) and chemical (UV-vis spectrophotometry) of 5 binary mixtures (morphine - haloperidol, morphine - metoclopramide, morphine - atropine, morphine – butyl scopolamine, morphine - ranitidine) at different concentrations, diluted in water, conditioned in glass and stored at 30 and 31°C under exposure to ambient light. The authors conclude that the mixtures appear stable but that the methodology used does not allow the identification of degradation products, so more sensitive and specific studies must be carried out.	28
Study of physical stability (visual inspection, pH) and chemical (HPLC) of mixtures of ondansetron with 12 other drugs diluted in physiological serum and packed in a plastic syringe (except the mix with propofol that is packed in glass). Syringes are stored at room temperature or refrigerated, protected from light for 24 hours. All mixtures are stable except the one containing droperidol, which precipitates rapidly when stored refrigerated, and remains stable at room temperature for only 8 hours.	29
Physical stability study (visual inspection, pH and osmolality) and chemical (HPLC) of binary mixtures of morphine hydrochloride with haloperidol, midazolam, dexamethasone or methylprednisolone for 28 days at 22°C. The order of mixing turned out to be important for the compatibility of the mixtures, which in general turned out to be compatible except for the mixture morphine + methylprednisolone and morphine + dexamethasone (it precipitates on some occasions).	30
Chemical stability study (HPLC) of mixtures of midazolam + fentanyl at different concentrations diluted in physiological serum in a polypropylene syringe and stored for 7 days at 5, 22 and 38°C were carried out by Wilson et al. The concentration of fentanyl remains stable, but midazolam degrades over time, the faster the higher the temperature. The authors conclude that the mixture is stable for 4 days at room temperature and 7 days refrigerated.	31
A review of morphine stability studies in different concentrations, diluents and primary packaging, as well as compatibility with other drugs. The authors conclude that most of the combinations evaluated are useful in the context of intensive care, but they cannot be extrapolated to PC, so more studies are required in this area.	32
Physical stability study (visual inspection, pH and osmolality) and chemical (HPLC) of ternary mixtures of morphine hydrochloride + haloperidol / midazolam + dexamethasone / methylprednisolone, diluted in	33

water and isotonized with physiological serum or glucose stored at 22°C protected from light during28 days. In all cases, the order of addition of the components is decisive, as well as the concentration, with a precipitate appearing when the concentrations are high.	
Study of physical (visual inspection) and chemical stability of mixtures at various concentrations of octreotide + diamorphine in polypropylene syringe stored at 37°C protected from light for 48 hours. The authors conclude that the mixtures are stable for at least 24 hours. Diamorphine is not marketed in Spain, so the results of this study are not included in the subsequent analysis.	34
Study of physical (visual inspection) and chemical (HPLC) stability of mixtures at various concentrations of dexamethasone + midazolam. When the concentration is high, when the components are mixed, precipitation occurs. However, at lower concentrations the mixture appears stable for at least 24 hours. In any case, the mixture should be used with caution.	35
In this paper there are a survey carried out in the United Kingdom and Ireland on the drugs used in PC by syringe infuser and the most commonly used concentrations. Information on the stability of the mixtures is not included.	36
Study of the compatibility and stability (visual inspection and HPLC-DAD) of morphine mixed with different drugs in physiological serum when it is packaged in a polypropylene syringe and stored for 96 hours at 25 or 4°C. The evaluated mixtures were: 1. Morphine + dexamethasone + octreotide 2. Morphine + dexamethasone + haloperidol 3. Morphine + octreotide + haloperidol + midazolam + famotidine 4. Morphine + haloperidol + famotidine + metoclopramide 5. Octreotide + haloperidol + famotidine + metoclopramide + dimenhydrinate Mix number 2 is incompatible because when mixing dexamethasone + haloperidol a white precipitate appears. Mixture number 3 is compatible at 25 ° C, but incompatible at 4 ° C due to crystallization of haloperidol. The rest of the mixtures are stable for 96h at both 4 and 25°C.	37
Physical stability study (visual evaluation of volume loss, colour change, turbidity and / or precipitation and pH) of mixtures of 2, 3, 4 and 5 components among the following: morphine, midazolam, haloperidol, butyl-scopolamine, dexamethasone, metoclopramide and tramadol, diluted in physiological saline and conditioned in an elastomeric infuser, stored at 25°C protected from light for 7 days. They evaluate a total of 86 mixtures of which 56 appear physically compatible. Unstable mixtures are those containing dexamethasone + haloperidol and / or midazolam. However, the dexamethasone + morphine mixture does appear physically stable. This work also includes a small clinical study of 18 of the stable mixtures in palliative patients for the control of symptoms, resulting in good control with all the mixtures tested, especially the one formed by morphine + midazolam + haloperidol + butyl scopolamine.	38
Study of physical compatibility of dexmedetomidine with other drugs simulating administration in Y.	39
Design of a research strategy to minimize the number of samples to be analyzed with the maximum information obtained about the physical (visual inspection) and chemical (HPLC) compatibility of binary mixtures of morphine hydrochloride with other drugs for 7 days at 22°C and 32°C.Mixtures with alizapride, atropine, dexamethasone, butyl scopolamine, metoclopramide, octreotide, and scopolamine are stable. The morphine + ranitidine mixture is incompatible when the morphine concentration is> 40mg / ml.	40
Study of physical stability (visual inspection) and chemical (HPLC) of mixtures of haloperidol + butyl scopolamine at various concentrations, diluted in physiological serum and conditioned in a polypropylene syringe, stored for 15 days at 4 and 25°C. Haloperidol precipitates when the concentration is ≥ 1.25 mg mL^{-1} when combined with butyl scopolamine. Butyl scopolamine concentrations less than 10 mg mL^{-1} with haloperidol at a concentration <0.625 mg mL^{-1} are stable at room temperature, but not at 4°C.	41
Study of physical stability (visual inspection) and chemical (HPLC-DAD) of drug mixtures in physiological serum conditioned in polypropylene syringe at 4 and 25°C for 96 hours: 1. Hydromorphine - midazolam - famotidine 2. Hydromorphone - metoclopramide - haloperidol 3. Hydromorphone - ketorolac - metoclopramide - famotidine 4. Hydromorphone - dimenhydrinate - haloperidol - famotidine - scopolamine Hydromorphone is not available parenterally in Spain.	42
Study of physical stability (visual inspection) and chemical (HPLC) of mixtures of both drugs in polypropylene syringe refrigerated or at room temperature for 6 months. Mixtures are compatible.	43
Study that shows that the mixture of both drugs is incompatible both physically (appearance of precipitate), and chemically (loss of active ingredient).	44

Study of physical stability (visual observation of signs of precipitation, turbidity, change in colour or opacity or gas production) and chemistry (HPLC) of the mixture of morphine and butyl scopolamine at different concentrations diluted in physiological serum and packed in polypropylene syringes, stored at 4 and 25°C protected from light. The authors conclude that the mixture is stable for at least 15 days under the conditions tested.	45
Study of physical stability (visual inspection) and chemical (HPLC) of ondansetron + methylprednisolone mixtures in 5% glucose or physiological serum in polyolefin bags for 24 hours at room temperature or for 48 hours refrigerated. The mixture is stable under refrigeration, but at room temperature methylprednisolone only remains stable for the first 7 hours when diluted in glucose serum, being stable for 24 hours if the diluent is physiological serum.	46
Physical stability study (visual inspection of volume loss, color change, turbidity, precipitation or gas production, pH change) and chemistry (HPLC) of binary mixtures of tramadol + haloperidol at different concentrations, diluted in physiological serum and conditioned in polypropylene syringe, stored at 4 and 25°C protected from light. All mixtures are physically and chemically stable under the evaluated conditions. In addition, a clinical study is carried out in 8 patients, with good local efficacy and safety results.	47
Study of physical stability (visual inspection, pH) and chemical (HPLC) of mixtures of both drugs at various concentrations diluted in physiological serum, packed in polypropylene syringes and stored at 4, 23 and 37°C for 192 hours. All the mixtures were compatible under the conditions studied during the 8 days of study.	48
Chemical stability study (HPLC) of mixtures of furosemide and dexamethasone at different concentrations diluted in physiological serum packed in polypropylene syringes and stored at 4 and 25°C protected from light. The mixtures are stable until the fifth day of study, regardless of the storage temperature. From that day on, the concentration of the active ingredients is less than 90% and also after 15 days the appearance of turbidity is observed.	49
Chemical stability study (HPLC) of a ternary mixture of morphine, haloperidol and butyl scopolamine at different concentrations diluted in physiological serum and packed in polypropylene syringes stored at room temperature and protected from light. The authors conclude that the mixtures are stable for at least 15 days. This work includes a clinical study in 21 patients to whom the drug mixture is administered, being effective in controlling symptoms in 17 of the 21 patients and safe in all of them.	50
Study evaluating the stability of parecoxib in a 24-hour portable IV elastomeric continuous infusion system, diluted with opiates (morphic chloride, meperidine or tramadol), antiemetics and physiological serum, for 24 hours; as well as, check the analgesic result, the appearance of side effects and the degree of satisfaction of patients who underwent major surgery susceptible to treatment with these drugs. Several tests were performed mixing parecoxib, opiates, antiemetics and physiological saline and its stability was observed for 24 hours by visual observation of the mixture repeatedly. The dilution always remained stable, clear, free of particles and transparent; Therefore, it was decided to use this mixture in the IV infuser for the treatment of postoperative pain, always under the supervision of an anaesthesiologist. A total of 118 patients were studied, the analgesic result was very good in 60 patients (50.85%); good at 40 (33.90%); regular in 12 (10.17%) and suspended treatment in 6 (5%) due to side effects. Side effects appeared in 30 cases (25%), 3 of them with treatment interruption.	51
Study of physical and chemical stability of binary mixtures of tramadol + butyl scopolamine diluted in physiological serum and conditioned in a polypropylene syringe at 4 and 25°C for 15 days. The mixtures are compatible.	52
Chemical stability study (HPLC) of mixtures of both drugs at various concentrations in physiological serum. The authors conclude that the mixtures are stable only for three days at room temperature, since the longer the components degrade.	53
Study of physical stability (visual inspection) and chemical (HPLC) of binary mixtures (haloperidol + scopolamine, haloperidol + morphine, haloperidol + midazolam, midazolam + morphine, midazolam + scopolamine) diluted in physiological serum or 5% glucose serum, conditioned in infuser and stored at room temperature, exposed to ambient light for 15 days. The haloperidol + scopolamine mixture is stable	54

for only one day and the haloperidol + morphine mixture becomes unstable from the 9th day. The rest of the mixtures are compatible under the conditions tested.	
Chemical stability study (HPLC) of mixtures at various concentrations of tramadol + dexamethasone in physiological serum packed in a polypropylene syringe and stored for 5 days at room temperature. The authors conclude that the mixture is compatible.	55
Informative bulletin on the risks to have when mixing parenteral drugs, with some examples of compatibilities and incompatibilities widely used in clinical practice, although it does not include references that allow evaluating whether these recommendations are supported by quality studies on the stability of mixtures.	56
Study of physical stability (visual inspection of colour change, precipitation or turbidity) and chemical (HPLC) of ternary mixtures of dexketoprofen + tramadol + haloperidol at a specific concentration (2.5mg / l dexketoprofen + 5 mg mL^{-1} tramadol + 0, 05 mg mL^{-1} haloperidol) diluted in physiological or glucose saline, packed in polyolefin bags and stored at different temperature combinations (frozen at -20°C, refrigerated at 4°C, at room temperature) and exposure to light. All mixtures are physically and chemically stable for 30 days.	57
Chemical stability study (HPLC) of tramadol + metoclopramide mixtures in 5% glucose serum packed in polyolefin bags and stored at 4°C for 32 days. The authors conclude that the mixture is compatible.	58
Compatibility study by visual inspection of drug mixtures commonly used in hematopoietic stem cell transplantation, simulating Y administration.	59
Stability study of the ternary mixture haloperidol-butyl-scopolamine-midazolam to establish its therapeutic validity. Ternary mixtures of haloperidol, butyl scopolamine, and midazolam were studied, using 5% glucose as vehicle, at concentrations of 0.2 and 0.8 mg mL^{-1} for haloperidol. For the other two components, the concentration (1.2 mg mL^{-1}) remained unchanged. The study was carried out under aseptic conditions, at room temperature, without photoprotection, in duplicate and for a period of 84 hours. As criteria of physical compatibility: change of colour, appearance of opalescence, variation of weight and pH. The chemical stability of the components was evaluated by HPLC. The T90 was used as a clinical validity parameter, considering for its calculation the value obtained by interpolating the lower limit of the 95% confidence interval of the representative line of linear kinetics, for a concentration of 90% of the initial concentration of the components. The values of the concentrations of the components were adjusted to a kinetics of order one. The T90 value obtained was not less than 72 hours in the studied mixtures. During the 84 hours that the test lasted, none of the mixtures showed a change in colour, appearance of opalescence, variation in weight or pH. The authors conclude that intravenous mixtures at the studied concentrations of haloperidol (up to 0.8 mg / ml), butyl scopolamine (1.2 mg mL^{-1}) and midazolam (1.2 mg mL^{-1}), prepared in 5% glucose, in Portable elastomeric infusion systems are physically compatible and chemically stable for at least 72 hours.	60
Study of physical stability (visual inspection, pH) and chemical (HPLC) of oxycodone in various diluents and packaging materials, as well as mixed with other drugs commonly used in PC. The mixtures were studied for 24 hours stored at 25 °C. They are all compatible except the mixture with cyclizine.	61
This article reflects on the meaning of words such as stability and compatibility and describes the possible effects that may affect them. Some works that have carried out studies of this type in the field of PC are also cited. The authors conclude that more experimental studies with sufficient methodological quality are necessary.	62
Description of a formulation that mixes haloperidol, butyl scopolamine and tramadol and demonstrates its stability for 30 days at room temperature, 9 days refrigerated or 45 days frozen.	63
Systematic review on the physical and chemical compatibility of drugs commonly used in intensive care to determine the possibility of administration in Y. The minimum stability time studied for Y-administration is considered insufficient to extrapolate the results for ICSC, so the results are not included in the subsequent analysis except for the documentation of incompatibility.	64
Physical stability study (determination of volume loss in Hamilton syringe, visual inspection of colour changes, turbidity, precipitation or gas formation and pH) and chemistry of ternary mixtures at various concentrations of tramadol + haloperidol + butyl scopolamine, diluted in physiological serum Conditioned in an infuser (type not specified) and stored at 25°C protected from light. All mixtures are physically and chemically stable under the evaluated conditions.	65

In addition, a clinical study is carried out in 28 patients, with good local efficacy and safety results.	
Study of physical compatibility of furosemide in parenteral mixtures. Furosemide was mixed with 12 drugs at a 1: 1 ratio, obtaining a total of 40 samples, evaluating the following variables at different times (minutes 0–15–30–60–120): pH of the mixture, determination of changes in the colour, turbidity and precipitation. For this, visual observation methods, pH measurement and absorption by spectrophotometry at 450–620 nm were used. Results: A total of 40 samples were made, 13 simple, 12 double and 15 triple. Those mixtures that did not present physical changes, variation in pH and changes in absorbance values were compatible. The authors conclude that furosemide is physically compatible with bicarbonate, heparin, insulin, morphine, nitro-glycerine, nimodipine, and thiopental solutions and incompatible with amiodarone, cisatracurium, haloperidol, midazolam, and urapidil.	66
Study of physical stability (visual inspection) and chemical (HPLC) of a mixture containing the four components indicated in the title in physiological serum, at room temperature for 48 hours. The authors conclude that the mixture is compatible.	67
It is a book published for the first time in 2002 and its third edition consulted (there is a later edition, from 2016, which has not been consulted). It contains a compilation of monographs of drugs used in PC and some compatibility tables of drug mixtures for use in ICSC by continuous syringe infusion (common method of subcutaneous infusion in Anglo-Saxon countries).References are consulted to include relevant information for our project.	68
Sheet for the elaboration of a mixture (Morphine 6-mg/mL, haloperidol 0.5- mg mL^{-1}, and hyoscine6- mg mL^{-1}, which is given 15 days of stability, although details of the methods used to establish this stability are not provided.	69
HPLC chemical stability study of mixtures at various concentrations of morphine + levomepromazine in water conditioned in polypropylene syringes and stored at 4°C protected from light, at room temperature (22°C) exposed to natural light and at 37°C exposed to artificial light. The authors conclude that while morphine remains stable under these conditions, levomepromazine degrades, at a higher rate the higher the storage temperature. The concentration of levomepromazine decreases correlatively with the appearance of its degradation product (sulfoxide) and physical changes (colour) are also seen.	70
Physical stability study (visual inspection to identify the presence of turbidity, precipitation, gas formation or colour change, pH measurement by pH meter) and chemistry (HPLC) of the morphine - ketorolac mixture at different concentrations, diluted in physiological serum, packaged in a polypropylene syringe and stored at 25°C protected from light. A physical stability study is also carried out (visual inspection to identify the presence of turbidity, precipitation, gas formation or colour change, pH measurement using a pH meter) of binary (methadone - ketorolac) and ternary (morphine – ketorolac – haloperidol / dexamethasone / metoclopramide / butyl scopolamine) prepared under the same conditions as the previous mixture. The authors conclude that morphine-ketorolac mixtures are chemically stable for 48 hours. These mixtures are compatible only at low concentrations and the order of mixing must be rigorous (morphine must be added last). Methadone-ketorolac mixtures are physically stable for 48 hours, a precipitate form when both components are mixed, but this dissolve when the diluent is added. It would be necessary to carry out a chemical stability study of this mixture to complete the information. Ternary mixtures are physically stable, but their chemical compatibility has not been established.	71
Study of the impact of the incompatibility of the drug mixture on its infusion through a filter. A mixture known as unstable is used and it is demonstrated despite not having visible particles because the flow is slowed by the retention of sub-visible particles in the filter.	72
Study in which a compatibility test is carried out between the most commonly used subcutaneous drugs in the Palliative Care Unit of the Oncology Service of the Central Hospital of the Armed Forces. Furosemide precipitates with most of the drugs used and ranitidine cannot be combined with levomepromazine or midazolam. The rest of the combinations are stable and facilitate the approach to the most frequently encountered symptoms in our clinical practice. It should be noted that subcutaneous dexamethasone is also widely used in our unit. It can only be mixed with 1% morphine hydrochloride, since with the rest of the drugs it precipitates, causing local irritation at the subcutaneous tissue level, which is why we always administer it by an independent subcutaneous route.	73

Study of physical stability (pH, colour change, appearance of gas and / or precipitate) and chemical (HPLC) of four drug mixtures (1 binary, morphine - midazolam, and three mixtures of three drugs) diluted in physiological saline and conditioned in elastomeric infuser kept at room temperature and refrigerated and under different conditions of exposure to light. Conclusions: mixtures containing levomepromazine degrade rapidly and mixtures containing morphine at high concentration may precipitate when stored refrigerated.	74
Study of physical stability (visual and photometric inspection) and chemical (HPLC) of drug mixtures with clonidine, hydroxybutyric acid, ketamine, lormetazepam, midazolam, piritramide and sufentanyl in physiological serum for 7 days. The mixtures of hydroxybutyric acid with ketamine, midazolam or piritramide are incompatible, as well as the mixture of clonidine with sufentanyl. The other couples studied are stable.	75
Study of physical stability (visual inspection, pH) and chemical (HPLC) of butorphanol + ropivacaine mixtures diluted in physiological serum and packed in polyolefin bags. They were stored for 15 days at 4°C and at room temperature. The authors conclude that the combination is compatible.	76
Guide that compiles the information available in the bibliography for healthcare personnel on the administration of drugs subcutaneously in PC patients of the Home Hospitalization Unit. It contains a summary table of 65 drugs by reviewing the technical reports of the manufacturing laboratories and other literature published by scientific organizations, in addition to the bibliographic search in Pubmed® and Micromedex®. Contains information on compatibility of mixtures in each drug.	77
The samples were prepared and diluted in NaCl 0.9% in elastomeric infuser in triplicate to obtain four different conditions of concentration and/or temperature of storage (concentration: 3.0 mg/mL - 2.0 mg/mL, 1.0 mg mL^{-1} – 0. mg mL^{-1} of morphine and furosemide respectively; temperature of storage 25°C and 37°C). The concentration of each constituent drug into different mixtures was periodically determined using a HPLC-UV method. The stability of the admixtures diluted in NaCl 0.9% are as follow: morphine - furosemide (3.0 mg mL^{-1}-2.0 mg mL^{-1}) is stable (retained >95% of their initial concentration) eight days at 25°C and two day at 37°C; (1.0 mg mL^{-1} - 0.6 mg mL^{-1}) is stable thirty days at 25°C and two day at 37°C.	78
The concentration of each constituent drug into different mixtures was periodically determined using a HPLC-UV method. The admixture of midazolam-furosemide prepared in NS and stored in infusers retained more than 95% of the initial drug concentrations during 24 hours and so they can use with security in palliative care during this period. These admixtures stored into glass are stable during more days.	79
The samples were prepared and diluted in NaCl 0.9% in elastomeric infusers in triplicate to obtain six different conditions of concentration and/or temperature of storage (concentration: 2000 mg/l - 2000 mg/l, 1000 mg L^{-1} - 600 mg L^{-1}, 600 mg L^{-1} - 600 mg L^{-1} of hyoscine N-butyl bromide and furosemide respectively; temperature of storage 25°C and 37°C). The concentration of each constituent drug into different mixtures was periodically determined using a HPLC-UV method.	80
Survey of pharmacists in the United Kingdom dedicated to PCs about the drug mixtures used or that could be used for their administration by ICSC. Multiple possible combinations are identified. Next, using a Delphi method, the 5 most interesting ones that must be analysed are prioritized:	5
Literature review of studies on stability of ondansetron preparations alone or mixed with other parenteral drugs. The authors conclude that the mixtures are compatible with 15 drugs and incompatible with 38 other drugs. The article has an extensive table with this detailed information.	81
Systematic review that includes 21 empirical studies, on 32 possible combinations between 24 different drugs at different concentrations. Most of the combinations are stable, midazolam being the drug with the most stability problems.	82
HPLC-UV method has been employed for the determination of the drugs. The concentrations of the admixtures were 0.15 mg mL^{-1} – 0.25 mg mL^{-1} and 0.3 mg mL^{-1} – 0.4 mg mL^{-1} of haloperidol and ondansetron respectively; temperature of storage 25°C and 37°C. From the results obtained we can conclude that the mixtures prepared in the conditions previously described are stable less of 48 hours.	83
The objective of this work is to evaluate the compatibility and stability of the mixtures of morphine and haloperidol prepared with NaCl 0.9% at different concentrations stored in elastomeric infusers at 25°C and 37°C and with protection of light. Mixtures concentrations were determined by a stability-indicating HPLC method. Morphine and haloperidol mixtures in saline solution are stable for at least three days when	84

stored in an elastomeric infuser at room temperature or near body temperature in a concentration range of 0.15-0.8 mg mL^{-1} and 0.3-3.0 mg mL^{-1} haloperidol-morphine respectively.	
Study of physical stability (visual inspection, pH) and chemical (HPLC) of the mixture of metoclopramide and midazolam diluted in physiological serum in polyethylene bags, stored at room temperature and not protected from light. The concentrations evaluated were 0.02 - 0.04, 0.06 - 0.12 and 0.12 - 0.27 mg mL^{-1} of metoclopramide and midazolam respectively. The mixtures remain stable during the 15 days of study.	85

Table 2 Results of the survey on the use of mixtures

Mixture	Utilization N (%)	Consumption (%)		Priority N (%)
		Frequent N (%)	Not frequent N (%)	
Morphine – Midazolam	38 (92.7)	38 (92.7)	-	33 (80.5)
Morphine – scopolamine	29 (70.7)	18 (43.9)	10 (24.4)	13 (31.7)
Morphine – butyl scopolamine	39 (95.1)	38 (92.7)	1 (2.4)	26 (63.4)
Morphine – metoclopramide	31 (75.6)	18 (43.9)	17 (41.5)	10 (24.4)
Morphine - haloperidol	35 (85.4)	23 (56.1)	12 (29.3)	15 (36.6)
Morphine – dexamethasone	15 (36.6)	11 (26.8)	5 (12.2)	12 (29.3)
Morphine – ketamine	0	-	-	-
Morphine – ondansetron	16 (39.0)	6 (14.6)	10 (24.4)	2 (4.9)
Morphine – octreotide	14 (34.1)	10 (24.4)	4 (9.8)	7 (17.1)
Morphine – levomepromazine	30 (73.2)	15 (36.6)	16 (39.0)	11 (26.8)
Morphine – furosemide	9 (22.0)	0	10 (24.4)	3 (7.3)
Midazolam – scopolamine	27 (65.9)	18 (43.9)	6 (14.6)	13 (31.7)
Midazolam – metoclopramide	25 (61.0)	14 (34.1)	12 (29.3)	7 (17.1)
Midazolam – haloperidol	33 (80.5)	15 (36.6)	16 (39.0)	7 (17.1)
Midazolam – ketamine	0	-	-	-
Midazolam – ondansetron	14 (34.1)	5 (12.2)	10 (24.4)	1 (2.4)
Midazolam – levomepromazine	24 (58.5)	9 (22.0)	15 (36.6)	6 (14.6)
Midazolam– butyl scopolamine	39 (95.1)	33 (80.5)	6 (14.6)	18 (43.9)
Midazolam – furosemide	7 (17.1)	0	8 (19.5)	1 (2.4)
Metoclopramide–butyl scopolamine	25 (61.0)	13 (31.7)	12 (29.3)	2 (4.9)
Metoclopramide – scopolamine	9 (22.0)	3 (7.3)	7 (17.1)	2 (4.9)
Haloperidol – tramadol	5 (12.2)	2 (4.9)	3 (7.3)	0
Haloperidol - ketamine	0	-	-	-
Haloperidol–butyl scopolamine	31 (75.6)	13 (31.7)	18 (43.9)	6 (14.6)
Haloperidol – octreotide	15 (36.6)	3 (7.3)	12 (29.3)	4 (9.8)
Haloperidol – ondansetron	14 (34.1)	5 (12.2)	10 (24.4)	4 (9.8)
Furosemide – metoclopramide	5 (12.2)	2 (4.9)	4 (9.8)	1 (2.4)
Furosemide – ondansetron	5 (12.2)	1 (2.4)	6 (14.6)	1 (2.4)

On the other hand, to identify the drug mixtures used and likely to be used in PC patients in Andalusia (our region) a survey was sent to the different healthcare professionals.

The surveys received were processed to obtain a prioritized general list of drug mixtures according to the following criteria: number of palliative units in which it is used, number of monthly units consumed throughout Andalusia and subjective priority assigned in each unit to the need for knowledge about its stability. It is also known what type of infusers is used most frequently in our autonomous community.

A total of 28 binary drug mixtures were included in the surveys, whose characteristics appear in Table 2.

Based on these data, a prioritized general list of drug mixtures is obtained according to the following criteria: number of palliative units in which it is used, frequent consumption by a greater number of units, and subjective priority assigned to each unit. Three of the mixtures that were asked are not useful for any of the respondents, so they will not be considered in the future (Table 3).

Table 3 Prioritized list of mixtures derived from the survey

Mixture	**Priority**
Morphine – midazolam	1
Morphine – butyl scopolamine	2
Midazolam – butyl scopolamine	3
Morphine - haloperidol	4
Morphine – scopolamine	5
Midazolam – scopolamine	6
Morphine – levomepromazine	7
Morphine – dexamethasone	8
Morphine – metoclopramide	9
Midazolam – haloperidol	10
Midazolam – metoclopramide	11
Morphine – octreotide	12
Haloperidol – butyl scopolamine	13
Midazolam – levomepromazine	14
Haloperidol – ondansetron	15
Haloperidol – octreotide	16
Morphine – furosemide	17
Metoclopramide – butyl scopolamine	18
Morphine – ondansetron	19
Metoclopramide – scopolamine	20
Midazolam – ondansetron	21
Furosemide – metoclopramide	22
Furosemide – ondansetron	23
Midazolam – furosemide	24
Haloperidol – tramadol	25

In addition, CP professionals added other proposed mixtures, listed below (Table 4).

Table 4 Other proposed mixtures by CP professionals

Binary mixtures	
Furosemide + butyl scopolamine	Granisetron + haloperidol
Dexamethasone + octreotide	Granisetron + haloperidol
Tramadol + butyl scopolamine	Metoclopramide + octreotide
Tramadol + midazolam	Diclofenac + ceftriaxone
Metoclopramide + octreotide	Phenobarbital + levetiracetam
Granisetron + metoclopramide	
Other mixtures	
Metamizole and other complex mixtures	Morphine + midazolam + scopolamine + haloperidol
Midazolam+ morphine +butyl scopolamine	Morphine + haloperidol + butyl scopolamine + midazolam
Levomepromazine + morphine + butyl scopolamine	Ceftriaxone + pyridostigmine
Midazolam + morphine + haloperidol+ butyl scopolamine	

Table 5 shows the results corresponding to the median of the usual dose ranges and the maximum doses of the drugs involved in the binary mixtures used in PC, as well as the minimum and maximum in parentheses.

Table 5 Usual dose range and maximum doses used by respondents

Drug	**Usual dose range (mg) Median (min – max)**		**Maximum dose (mg) Median (min – max)**
	Lower range	**Upper range**	
Morphine	20 (5-60)	70 (10-1600)	Not applicable
Midazolam	17.5 (5-60)	47.5 (10-200)	120 (15-250)
Scopolamine	1.75 (0.5-2.5)	2 (1.5-6)	2.5 (1.5-6)
Butyl scopolamine	60 (10-160)	80 (20-240	120 (60-240)
Metoclopramide	30 (10-40)	40 (10-90)	60 (10-90)
Haloperidol	2.5 (1.5-20)	5 (2.5-40)	15 (2.5-100)
Dexamethasone	4 (2-12)	16 (8-40)	24 (16-80)
Ondansetron	12 (4-32)	24 (8-32)	24 (12-32)
Octreotide	0.3 (0.1-0.4)	0.3 (0.1-0.9)	0.8 (0.2-6)
Levomepromazine	25 (12.5-100)	100 (25-300)	200 (25-300)
Furosemide	40 (20-120)	70 (20-260)	160 (40-600)
Tramadol	100 (50-200)	300 (50-400)	350 (150-450)

Below is a brief descriptive analysis of the infusers (type, volume, and duration) used for subcutaneous infusion in PC (Table 6).

Table 6 Types of infusers used by respondents

Infuser type				
Elastomeric	**Mechanical**	**Atmospheric pressure**	**Other**	
36 (87.80%)	2 (4.87%)	2 (4.87%)	0.00%	
Volume				
65 ml	96 ml	130 ml	275 ml	Other**
14 (34.14%)	12 (29.26%)	7 (17.07%)	10 (24.39%)	14 (34.14%)
Duration				
1 day	2 days	5 days	7 days	Other***
17 (41.46 %)	14 (34.14%)	25 (60.97%)	21 (51.22%)	12 (29.26%)

* The answers are not exclusive. ** From 24, 48, 50, 60, 100, 120, 150, 255, 300 mL and variable flow. *** From 3, 4, 8, 10 days and adjustable from 1 to 3 mL / h.

Following this order (Table 3), the information available on their stability is described, referencing where the information comes. The evidence found is classified as high, medium or low quality according to the following criteria:

- High quality of evidence: when there is at least one published study that demonstrates the chemical and physical stability of the components in physiological serum and in the infuser
- Average quality of evidence: when chemical and physical stability is demonstrated under different conditions (mixtures in glucose serum or water, conditioned in polypropylene, glass, ...)
- Low quality of evidence: when we only have evidence of physical stability, or refers to individual experiences without an adequate protocol for the study of stability.

Legend

- F = Physics
- Q = Chemistry
- SSF = Physiological serum
- G5% = Glucose serum 5%
- RT = Room temperature
- PPS = Polypropylene syringe

2.1. Morphine – midazolam

Table 7 Compatible mixture, high quality of evidence

Drug **A: Morphine HCl** **B: Midazolam**	**Dose (mg)**	**Vol. (ml)**	**Concentration (mg/ml)**	**Diluent**	**Packaging material**	**Result**	**Ref**
A	420	250	1.68	SSF	Infuser	Compatible (F) 7 days, RT	38
B	105		0.42				
A	300	60	5.00	SSF	Infuser	Compatible (F) 5 days, RT	38
B	75		1.25				
A	18	60	0.30	SSF and G5%	Infuser	Compatible (FQ) 15 days, RT	54
B	9		0.15				

Other references: 11, 17, 40

2.2. Morphine – butyl scopolamine

Table 8 Compatible mixture, average quality of evidence

Drug A: Morphine HCl B: Butyl scopolamine	Dose (mg)	Vol. (ml)	Concentration (mg/ml)	Diluent	Packaging material	Result	Ref
A	100	60	1.67	SSF	PPS	Compatible (FQ) 15 days RT and cool	45
B	200		3.33				
A	100	60	1.67	SSF	PPS	Compatible (FQ) 15 days RT and cool	45
B	300		5.00				
A	100	60	1.67	SSF	PPS	Compatible (FQ) 15 days RT and cool	45
B	400		6.67				
A	300	60	5.00	SSF	PPS	Compatible (FQ) 15 days RT and cool	45
B	300		5.00				
A	300	60	5.00	SSF	PPS	Compatible (FQ) 15 days RT and cool	45
B	400		6.67				
A	600	60	10.00	SSF	PPS	Compatible (FQ) 15 days RT and cool	45
B	200		3.33				
A	600	60	10.00	SSF	PPS	Compatible (FQ) 15 days RT and cool	45
B	300		5.00				
A	600	60	10.00	SSF	PPS	Compatible (FQ) 15 days RT and cool	45
B	400		6.67				
A	420	250	1.68	SSF	Infuser	Compatible (F) 7 days RT	38
B	420		1.68				
A	300	60	5.00	SSF	Infuser	Compatible (F) 5 days RT	38
B	200		3.33				

Other references: 28, 40, 50

2.3. Midazolam – butyl scopolamine

Table 9 Compatible mixture, average quality of evidence

Drug A: Midazolam B: Butylscopolamine	Dose (mg)	Vol. (ml)	Concentration (mg/ml)	Diluent	Packaging material	Result	Ref
A	105	250	0.42	SSF	Infuser	Compatible (F) 7 days RT	38
B	420		1.68				
A	75	60	1.25	SSF	Infuser	Compatible(F) 5 days RT	38
B	300		5.00				
A	72	60	1.20	G5%	Infuser	Compatible (FQ) 3 days RT, ternary mixture with haloperidol	60
B	72		1.20				

Other reference: 73

2.4. Morphine – haloperidol

Table 10 Compatible mixture, high quality of evidence

Drug A: Morphine HCl B: Haloperidol	Dose (mg)	Vol. (ml)	Concentration (mg/ml)	Diluent	Packaging material	Result	Ref
A	420	250	1.68	SSF	Infuser	Compatible (F) 7 days, RT	38
B	112		0.45				
A	300	60	5.00	SSF	Infuser	Compatible (F) 5 days, RT	38
B	80		1.33				
A	48	60	0.8	SSF	Infuser	Compatible (FQ) 8 days, RT and 37°C	84
B	9		0.15				
A	96	60	1.60	SSF	Infuser	Compatible (FQ) 4 days, RT and 37°C	84
B	9		0.15				
A	180	60	3.00	SSF	Infuser	Compatible (FQ) 3 days, RT and 37°C	84
B	18		0.30				

Other references: 8, 17, 28, 30, 50, 54, 73

2.5. Morphine – scopolamine

Table 11 Compatible mixture, average quality of evidence

Drug A: Morphine HCl B: Scopolamine	Dose (mg)	Vol. (ml)	Concentration (mg/ml)	Diluent	Packaging material	Result	Ref
A	--	--	50.00	water	--	Compatible (Q) 14 days, RT and 37°C	10
B	--		0.50				

Other reference: 40

2.6. Midazolam – scopolamine

Table 12 Compatible mixture, high quality of evidence

Drug A: Midazolam B: Scopolamine	Dose (mg)	Vol. (ml)	Concentration (mg/ml)	Diluent	Packaging material	Result	Ref
A	18,6	60	0.31	SSF, G5%	Infuser	Compatible (FQ) 15 days, RT	54
B	75		1.25				

2.7. Morphine – levomepromazine

Incompatible mixture, low quality of evidence

Other references: A study carried out with the morphine sulphate (70) shows that the mixture is not compatible. Another study with morphine hydrochloride, but in a ternary mixture with midazolam, is also incompatible (74). In some tertiary sources (68, 73) the mixture appears as compatible, but the experimental studies that demonstrate it have not been located.

2.8. Morphine – dexamethasone

Table 13 Compatible mixture, average quality of evidence

Drug A: Morphine HCl B: Dexamethasone	Dose (mg)	Vol. (ml)	Concentration (mg/ml)	Diluent	Packaging material	Result	Ref
A	420	250	1.68	SSF	Infuser	Compatible (F) 7 days, RT	38
B	52,5		0.21				
A	300	60	5.00	SSF	Infuser	Compatible (F) 5 days, RT	38
B	37,5		0.63				

Other references: 8, 30, 37, 40

2.9. Morphine – metoclopramide

Table 14 Compatible mixture, average quality of evidence

Drug A: Morphine HCl B: Metoclopramide	Dose (mg)	Vol. (ml)	Concentration (mg/ml)	Diluent	Packaging material	Result	Ref
A	420	250	1.68	SSF	Infuser	Compatible (F) 7 days, RT	38
B	280		1.12				
A	300	60	5.00	SSF	Infuser	Compatible (F) 5 days, RT	38
B	200		3.33				

Other references: 8, 21, 28, 40

2.10. Midazolam – haloperidol

Table 15 Compatible mixture, high quality of evidence

Drug A: Midazolam B: Haloperidol	Dose (mg)	Vol. (ml)	Concentration (mg/ml)	Diluent	Packaging material	Result	Ref
A	105	250	0.42	SSF	Infuser	Compatible (F) 7 days, RT	38
B	52,5		0.21				
A	75	60	1.25	SSF	Infuser	Compatible (F) 5 days, RT	38
B	37,8		0.63				
A	37,8	60	0.63	SSF, G5%	Infuser	Compatible (FQ) 15 days, RT	54
B	12,6		0.21				
A	72	60	1.20	G5%	Infuser	Compatible (FQ) 3 days, RT, ternary mixture with butyl scopolamine	60
B	12		0.20				
A	72	60	1.20	G5%	Infuser	Compatible (FQ) 3 days, RT, ternary mixture with butyl scopolamine	60
B	48		0.8				

Other reference: 73

2.11. Midazolam – metoclopramide

Table 16 Compatible mixture, average quality of evidence

Drug A: Midazolam B: Metoclopramide	Dose (mg)	Vol. (ml)	Concentration (mg/ml)	Diluent	Packaging material	Result	Ref
A	125	250	0.50	SSF	Infuser	Compatible (F) 7 days, RT	38
B	275		1.11				
A	90	60	1.50	SSF	Infuser	Compatible (F) 5 days, RT	38
B	200		3.33				
A	20	500	0.04	SSF	PE	Compatible (FQ) 15 days, RT	85
B	10		0.02				
A	60	500	0.12	SSF	PE	Compatible (FQ) 15 days, RT	85
B	30		0.06				
A	135	500	0.27	SSF	PE	Compatible (FQ) 15 days, RT	85
B	60		0.12				

Other reference: 73

2.12. Morphine – octreotide

Compatible mixture, low quality of evidence

Apparently compatible, so it appears in some references (37, 40, 68) but the detailed information is not available.

2.13. Haloperidol – butyl scopolamine

The concentration of the mixture is important to ensure stability (it should be less than 1.25 mg mL^{-1} haloperidol). It appears that dilution in glucose serum and room temperature favour stability.

Table 17 Compatible mixture, high quality of evidence

Drug A: Haloperidol B: Butyl scopolamine	Dose (mg)	Vol. (ml)	Concentration (mg/ml)	Diluent	Packaging material	Result	Ref
A	37.2	60	0.62	SSF	Infuser	Compatible (F) 5 days, RT	38
B	300		5.00				
A	52.5	250	0.21	SSF	Infuser	Compatible (F) 7 days, RT	38
B	420		1.68				
A	75	60	1.25	SSF	PPS	Incompatible, haloperidol precipitate	41
B	600		10.00				
A	37.5	60	0.625	SSF	PPS	Compatible (FQ) 15 days, RT, no refrigerate	41
B	600		10.00				

Other references: 50, 60, 65, 73

2.14. Midazolam – levomepromazine

Table 18 Inconclusive data, low quality of evidence

Drug A: Midazolam B: Levomepromazine	Dose (mg)	Vol. (ml)	Concentration (mg/ml)	Diluent	Packaging material	Result	Ref
A	90	130	0.69	SSF	Infuser	Compatible (FQ) 5 days and cool, 48 h TA. Always protect from the light. Ternary mixture study with morphine HCl	74
B	150		1.15				
A	300	130	2.30	SSF	Infuser	Incompatible in ternary mixture with morphine HCl	74
B			3.75				

Other reference: 73

The study by Fernández Campos [74] (shows that the protection from light offered by the infuser used (Baxter CE infuser LV 5ml / h System 2C1009K) does not offer sufficient protection against light. Since levomepromazine is a photosensitive drug, if the mixture is used under the tested conditions that have been shown to be stable, it is necessary to protect from light with an additional element.

2.15. Haloperidol – ondansetron

Table 19 Incompatible mixture, high quality of evidence

Drug A: Haloperidol B: Ondansetron	Dose (mg)	Vol. (ml)	Concentration (mg/ml)	Diluent	Packaging material	Result	Ref
A	9	60	0.15	SSF	Infuser	Incompatible, precipitate at 48 h	83
B	15		0.25				
A	18	60	0.30	SSF	Infuser	Incompatible,precipitate at 48 h	83
B	24		0.40				

2.16. Haloperidol – octreotide

Table 20 Compatible mixture, low quality of evidence

Drug A: Haloperidol B: Octreotide	Dose (mg)	Vol. (ml)	Concentration (mg/ml)	Diluent	Packaging material	Result	Ref
A	5	100	0.5	SSF	PPS	Compatible (FQ) 96h RT, no refrigerate. Mixture with five drugs with morphine, famotidine and midazolam	37
B	0.1		0.01				

2.17. Morphine – furosemide

Table 21 Compatible mixture, high quality of evidence

Drug A: Morphine HCl B: Furosemide	Dose (mg)	Vol. (ml)	Concentration (mg/ml)	Diluent	Packaging material	Result	Ref
A	180	60	3.00	SSF	Infuser	Compatible (FQ) 8 days, RT and 2 days37°C	78
B	120		2.00				
A	60	60	1.00	SSF	Infuser	Compatible (FQ) 30 days, RT and 2 days 37°C	78
B	36		0.60				

Other references: 66, 73

2.18. Metoclopramide- butyl scopolamine

Table 22 Compatible mixture, low quality of evidence

Drug A: Metoclopramide B: Butyl scopolamine	Dose (mg)	Vol. (ml)	Concentration (mg/ml)	Diluent	Packaging material	Result	Ref
A	200	60	3.33	SSF	Infuser	Compatible (F) 5 days, RT	38
B	300		5.00				
A	275	250	1.11	SSF	Infuser	Compatible (F) 7 days, RT	38
B	420		1.68				

2.19. Morphine – ondansetron

Information not available, the references found uses morphine in the sulphate form, in which it is apparently compatible [15, 29].

2.20. Metoclopramide – scopolamine

Information not available

2.21. Midazolam – ondansetron

Table 23 Compatible mixture, low quality of evidence

Drug A: Midazolam B: Ondansetron	Dose (mg)	Vol. (ml)	Concentration (mg/ml)	Diluent	Packaging material	Result	Ref
A	58.3	35	1.67	SSF	PPS	Compatible (FQ) 24 h RT	29
B	46.5		1.33				

2.22. Furosemide – metoclopramide

Lack of information in experimental studies. In some databases the mix is defined as incompatible.

2.23. Furosemide – ondansetron

Lack of information in experimental studies. In some databases the mix is defined as incompatible.

2.24. Midazolam – furosemide

Table 24 Compatible mixture, high quality of evidence. Stability in glass is higher than infuser.

Drug A: Midazolam B: Furosemide	Dose (mg)	Vol. (ml)	Concentration (mg/ml)	Diluent	Packaging material	Result	Ref
A	18	60	0.30	SSF	Infuser	Compatible (FQ) 2 days RT, 24h and 37°C	79
B	36		0.60				
A	18	60	0.30	SSF	Infuser	Compatible (FQ) 24h RT and 37°C	79
B	42		0.70				
A	21	60	0.35	SSF	Infuser	Compatible (FQ) 24h RT and 37°C	79
B	36		0.60				

Other references: 66, 72

2.25. Tramadol - haloperidol

Table 25 Compatible mixture, high quality of evidence

Drug A: Tramadol B: Haloperidol	Dose (mg)	Vol. (ml)	Concentration (mg/ml)	Diluent	Packaging material	Result	Dose (mg)	Ref
A	500	60	8.33	SSF		PPS	Compatible (FQ) 15 days RT and cool	47
B	12.5		0.21					
A	1000	60	16.67	SSF		PPS	Compatible (FQ) 15 days RT and cool	47
B	25		0.42					
A	2000	60	33.33	SSF		PPS	Compatible (FQ) 15 days RT and cool	47
B	37.5		0.63					

Other references: 38, 57, 63, 65

2.26. Furosemide – butyl scopolamine

Table 26 Compatible mixture, high quality of evidence

Drug A: Furosemida B: Butyl scopolamine	Dose (mg)	Vol. (ml)	Concentration (mg/ml)	Diluent	Packaging material	Result	Ref
A	2000	60	33.33	SSF	Infuser	Compatible (FQ) 2 days, RT and 37°C	80
B	2000		33.33				
A	600	60	10	SSF	Infuser	Compatible (FQ) 8 days, RT, 2 days 37°C	80
B	1000		16.67				
A	600	60	10	SSF	Infuser	Compatible (FQ) 12 days, RT, 3 days 37°C	80
B	600		10				

2.27. Tramadol – butyl scopolamine

Table 27 Compatible mixture, average quality of evidence

Drug A: Tramadol B: Butyl scopolamine	Dose (mg)	Vol. (ml)	Concentration (mg/ml)	Diluent	Packaging material	Result	Ref
A	500	60	8.33	SSF	PPS	Compatible (FQ) 7 days, RT and cool	52
B	200		3.33				
A	500	60	8.33	SSF	PPS	Compatible (FQ) 7 days, RT and cool	52
B	400		6.67				
A	1000	60	16.67	SSF	PPS	Compatible (FQ) 7 days, RT and cool	52
B	200		3.33				
A	1000	60	16.67	SSF	PPS	Compatible (FQ) 7 days, RT and cool	52
B	300		5.00				
A	1000	60	16.67	SSF	PPS	Compatible (FQ) 7 days, RT and cool	52
B	400		6.67				
A	2000	60	33.33	SSF	PPS	Compatible (FQ) 7 days, RT and cool	52
B	200		3.33				
A	2000	60	33.33	SSF	PPS	Compatible (FQ) 7 days, RT and cool	52
B	300		5.00				
A	2000	60	33.33	SSF	PPS	Compatible (FQ) 7 days, RT and cool	52
B	400		6.67				

Other reference: 38

2.28. Tramadol – dexamethasone

Table 28 Compatible mixture, average quality of evidence

Drug A: Tramadol B: Butyl scopolamine	Dose (mg)	Vol. (ml)	Concentration (mg/ml)	Diluent	Packaging material	Result	Ref
A	500	60	8.33	SSF	PPS	Compatible (FQ) 5 days, RT and cool	55
B	20		0.33				
A	2000	60	33.33	SSF	PPS	Compatible (FQ) 5 days, RT and cool	55
B	200		3.33				

Other reference: 38

2.29. Haloperidol – scopolamine

Table 29 Compatible mixture, high quality of evidence

Drug A: Haloperidol B: Scopolamine	Dose (mg)	Vol. (ml)	Concentration (mg/ml)	Diluent	Packaging material	Result	Ref
A	50	60	0.83	SSF, G5%	Infuser	Compatible (FQ) 1day RT	54
B	40		6.66				

2.30. Haloperidol – metoclopramide

Table 30 Compatible mixture, average quality of evidence

Drug A: Haloperidol B: Metoclopramide	Dose (mg)	Vol. (ml)	Concentration (mg/ml)	Diluent	Packaging material	Result	Ref
A	52.5	250	0.21	SSF	Infuser	Compatible (F) 7 days, RT	38
B	280		1.12				
A	37.5	60	0.63	SSF	Infuser	Compatible (F) 5 days, RT	38
B	200		3.33				

2.31. Midazolam – dexamethasone

Incompatible mixture [35, 38, 44].

2.32. Haloperidol – dexamethasone

Incompatible mixture [37, 38].

2.33. Morphine – ranitidine

Incompatible mixture if morphine concentration is higher than 40 mg mL^{-1} [40]. No stability data available at lower concentration.

3. Discussion

The use of drugs to control symptoms in PCs is a fundamental pillar in comprehensive care for people suffering from an advanced or terminal illness in a context of special vulnerability. It is a challenge for professionals and caregivers to try to alleviate symptoms effectively, while maintaining maximum patient comfort.

Very frequently, the subcutaneous route is used for the administration of medications to control symptoms. When the oral route is not available for some reason, the subcutaneous route is an alternative route that has proven to be effective and safe, as well as being well accepted by patients and caregivers for administration at home, thus avoiding admissions solely motivated by drug therapy.

Subcutaneous drug delivery can be done intermittently, by bolus delivery, or continuously, using infusers or infusion pumps. In the latter case, constant levels of drug in plasma are obtained and the autonomy of the patient and her family is facilitated since the time that the medication that is administered through the infuser lasts ranges from 24 hours to several days.

Some barriers that arise when it comes to finding bibliography that supports this clinical practice are: 1) SC administration is not included in the technical specifications of most drugs; 2) The type of infusion pump used is different depending on the geographic area, elastomeric infusers being the most widely used in our environment, while in Anglo-Saxon countries they usually use electronic syringe infusers. The latter is of great importance, since as seen in the results of the bibliographic search, most of the stability data come from studies in which the mixture is stored in a polypropylene syringe, and not in an elastomeric infuser, therefore that the extrapolation of the data may lead to certain biases.

The drugs most used in clinical practice are analgesics, anxiolytics, diuretics, corticosteroids and antiemetics, among others. Thus, the most used are morphine, butyl scopolamine, midazolam, metoclopramide and haloperidol, and to a lesser extent levomepromazine, furosemide, tramadol, dexamethasone, scopolamine, ondansetron and octreotide.

Different combinations of them may be of interest in the particular treatment of each patient, depending on the symptoms to be treated. In general, it is not recommended to mix more than 3 drugs in the same infuser, and it should be verified that the stability of the mixture has been previously documented.

In order to know the drug mixtures that are used most frequently in our environment and to focus our effort on those whose impact was more positive for patients in our environment, a survey was designed by which the most frequently used drug mixtures were identified. as well as the doses used for the medications and the type of infuser used.

One difficulty that we encountered when conducting the survey was the identification of support teams and PC units in Andalusia, with eminently hospital units, others dependent on primary care and other mixed. Although all of them were contacted, the units that care for patients through hospital admission did not usually use the subcutaneous route for drug administration, given the accessibility for the use and care of the intravenous route while the patient is admitted.

On the other hand, it was not specified that the answers had to be individual for each professional, so that in some units the answer was joint in the name of the unit. Thus, a total of 42 responses were received, from 14 nuclei that regularly use ICSC and 12 others that use other forms of drug administration. We are missing information from another 20 nuclei for which no response was received despite the reminder. The answer being completely voluntary, obtaining a response from 56.5% of the nuclei contacted can be considered an optimal level of participation, although we would have preferred it to be higher.

Regarding the type of unit that the ICSC usually uses, we can say that the majority corresponds to home support teams, in which 80% of the surveys received confirmed their interest in this administration route. This percentage drops to 62.5% in mixed teams and is barely 12.5% in hospital PC units.

Therefore, it is demonstrated that the interest of the administration by ICSC is fundamentally in the treatment of those patients who reside at home, more than in those who are admitted to hospitals.

Regarding the composition of the mixtures, the most frequently used, as expected, are those that contain morphine and / or midazolam. Apart from these two components, other drugs such as haloperidol, butyl-scopolamine, metoclopramide, ondansetron or furosemide are also often used in mixtures. Scopolamine, tramadol, octreotide, and dexamethasone appear more occasionally.

Ketamine, despite being included in the Manual for the Use of the Subcutaneous Route in Palliative Care, is not used by any of the professionals who answered the survey.

Other medications suggested by the survey participants are different combinations with tramadol and granisetron, as well as more complex mixtures of three or more components.

The answers regarding the doses used of the drugs allow us to have the information on the use in routine practice when designing the experimental studies, as they serve as a reference for the selection of the concentrations to be tested, simulating the next scenarios. to clinical practice in terms of container size and duration of the infusion.

Finally, regarding the system used for infusion, the use of elastomeric infusers is clearly predominant, although there are also some units that use mechanical or atmospheric pressure infusers. The sizes of the infusers used are varied, from 24 to 300 mL and the durations range from 1 to 10 days, the most frequent being 5, 7 and 1 day.

The information obtained gives us a vision close to the healthcare reality that is experienced day by day, patient by patient, so that the following steps in the development of this project have been carried out considering the preferences expressed by the professionals who belong to the PC network of the Autonomous Community of Andalusia.

In daily practice, it is common to resort to certain databases that collect this type of information. Some are CP specific, such as palliativedrugs.com; and other more general ones on drugs such as micromedex or stabilis.org. These were included in the design of the bibliographic search as they facilitated the task of locating originals of interest, to a greater extent than the result obtained through the search carried out in Pubmed and Embase.

Of the total of shortlisted articles, only references enclosed met the inclusion criteria. The most frequent reasons for exclusion were that the objective of the study was not related to the stability of the mixture or that the active principle was not marketed in Spain.

In any case, the information derived from the selected articles has been evaluated to decide whether the results can be extrapolated to our particular case. High quality of evidence is considered when we have a quality study that determines the physical and chemical compatibility of the mixture in the conditions most similar to those of our practice, in relation

to diluent (preferably physiological serum), conditioning (preferably in infuser), storage temperature, concentration of active ingredients, etc.

At this point, it is important to emphasize again that the information from English-speaking countries is usually oriented to the administration of drugs packaged in a polypropylene syringe, so that stability in an elastomeric infuser is often not available.

In addition to simulating the storage conditions of the drug mixture, the quality of published studies should be assessed. The reference guide for determining the drugs par excellence is the pharmacopoeia; however, it is not useful on many occasions in the clinical setting in which doubts arise that cannot be answered by the tests proposed in the monographs of said document. In the absence of a national guideline for the study of the stability of the preparations prepared in our field, we have taken as a reference the recommendations of the French Society of Clinical Pharmacy in this regard, both for the evaluation of the studies derived from the bibliographic search and for the design of the studies that we have carried out ourselves.

Some studies initially provide results of physical compatibility. In these cases, when it is shown that the mixture is incompatible, the information can be considered relevant, and the conclusion will be that under the conditions tested that mixture is incompatible and therefore should not be carried out. However, when the result is of physical compatibility, the opposite cannot be affirmed, since we do not know if a process of chemical instability occurs that we are not detecting. For this reason, the information is preferably selected from the studies that include the determination of both physical compatibilities, for which visual inspection and pH determination are usually used, as well as chemical compatibility, for which it is usually used the evaluation of the remaining amount of each of the active principles by HPLC, establishing the margin at 90-95% of active principle to consider the mixture as stable, as well as the absence of signals from degradation products.

In the bibliographic search we have also found another difficulty when extrapolating the data, and that is that the morphine tested in many cases is the sulphate salt and in some cases the tartrate salt, while the one we have available in Spain for the parenteral route is the hydrochloride salt. We do not know if the compatibility of both salts with other drugs is similar, so the evidence derived from studies carried out with a different salt should be evaluated with caution.

On the other hand, the conditioning used to carry out the studies seems very important [86] and we have also been able to verify in the experimental studies, the conditioning in an infuser reduces the compatibility time of the mixtures, with respect to the times that remain stable in other continents such as glass or polypropylene. The authors think that perhaps the force to which the mixture is subjected due to the shrinkage of the elastomer can accelerate the precipitation reactions of the poorly soluble active principles, since this is the sign of incompatibility that we have found most frequently in the experimental analysis.

The storage temperature is also an aspect to consider: it is essential to know the stability of the mixture at room temperature (25℃ +/- 2℃, it is the temperature established as room temperature by the methodological guidelines for the study of stability).

If the mixtures are to be prepared in advance in a parenteral mixing unit, for example in a hospital pharmacy, it might be interesting to know how long they can be stored in refrigeration, to limit possible microbial contamination.

But, in addition, in our case, as we intend to use the mixture in a portable infuser in contact with the patient's skin, it is also interesting to know the stability at a temperature close to body temperature. The mixture must be shown to be stable at this temperature for at least the duration of the infusion.

Another limitation of the review is due to publication bias, which is that some mixtures have probably been tested, but when negative results were obtained, they could not be published in scientific journals.

The fundamental conclusions derived from the bibliographic search are:

- Medicines that have a similar pH are usually compatible, the most alkaline being the ones that often show the greatest compatibility problem since most solutions are acidic.
- It is important to protect from light due to the photosensitivity of haloperidol and morphine, among others. When some of the components of the mixture are photosensitive, it is recommended to use some additional light protection system to the infuser itself, since the protection offered by the infuser is not sufficient in some cases.

- Haloperidol reduces the stability of the mixture, especially when used at high concentration or when refrigerated. Also, mixtures containing morphine can precipitate when refrigerated.
- Dexamethasone appears to be compatible with acidic compounds such as ketamine, metoclopramide and ranitidine, but it can precipitate at certain concentrations with haloperidol, midazolam and morphine due to the change in pH. For this reason, dexamethasone frequently destabilizes mixtures, inducing precipitation. Sometimes it is possible to resuspend the precipitate, especially if the concentration is not high and this component is the last to be added. In any case, many authors recommend administering dexamethasone always separately, to avoid this phenomenon.
- Midazolam and levomepromazine are also sensitive components, degrading with some ease in some mixtures, so they should never be used if the stability of the mixture has not been previously verified.
- The bibliographic review has allowed us to identify drug mixtures with sufficient evidence of physical and chemical stability to recommend their use in PC: mixtures of morphine with midazolam, butyl scopolamine or metoclopramide, mixtures of midazolam with butyl scopolamine, scopolamine, haloperidol or metoclopramide, and other mixtures such as haloperidol plus butyl scopolamine (taking care not to exceed the concentration of 1.25 mg / ml of haloperidol), haloperidol plus scopolamine, metoclopramide plus butyl scopolamine (evidence of physical compatibility only) or tramadol plus haloperidol, butyl scopolamine or dexamethasone (the mixtures with tramadol have evidence of physical and chemical stability in a polypropylene syringe, but not in an infuser).

Also, the mixtures that are not compatible and that therefore we should not recommend are: morphine - levomepromazine, midazolam - dexamethasone, haloperidol - dexamethasone, morphine - ranitidine.

For the other combinations, we do not have studies or these are not of sufficient quality to recommend their use in the context of PCs.

For all the above, the results improve:

- Patient safety because it allows the identification of mixtures that can be used and those that should be avoided for SC administration
- The pharmacotherapeutic quality of the patients to whom these drugs are administered, as there is an evidence-based foundation that guarantees that this practice is correct.
- Efficiency in the procedures for preparing mixtures, because with the available information it is possible to consider which mixtures can be prepared in advance and stored until use and which require immediate preparation before use, so that it allows the scheduling activities and decreases activity on demand
- The efficiency of the system, avoiding the admission of patients to hospital beds caused by the need for parenteral administration of drugs
- The humanization of care for palliative patients, because it allows home care for them and avoids hospital admissions.

4. Conclusion

The administration of drug mixtures in the infuser by subcutaneous route is of interest for non-admitted patients who receive assistance from home support teams, in whom access to the intravenous route is difficult.

The drug mixtures that arouse the most interest to the professionals surveyed are those that contain morphine and / or midazolam. Other medications that are of interest are haloperidol, butyl scopolamine, metoclopramide, ondansetron, and furosemide, among others.

The available evidence on the stability of mixtures is of low quality as there are few studies carried out in infusers. Older studies are limited to studying physical compatibility, without providing chemical compatibility data. The studies of Anglo-Saxon countries are carried out mainly in polypropylene syringes, since in these places the use of elastomeric infuser is not widespread. The extrapolation of the results is controversial, since the pressure exerted by the elastomer accelerates the precipitation and degradation reactions.

Compliance with ethical standards

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Disclosure of conflict of interest

The authors have declared that no competing interest exists.

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