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Short comunication

Physicochemical compatibility between ketoprofen lysine salt injections (Artrosilene®) and pharmaceutical products frequently used for combined therapy by intravenous administration

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Abstract

Ketoprofen lysine salt (Artrosilene® Fiale) is a non-steroidal anti-inflammatory agent frequently administered by intravenous infusion in association regimen with other drugs, such as steroidal anti-inflammatory, anti-hemorrhagic, anti-spastic, anti-ulcer, and antibacterial drugs. The aim of this study was to investigate the physicochemical compatibility between ketoprofen lysine salt (Artrosilene® Fiale) and other injectable drugs frequently used in association. Physicochemical properties of ketoprofen lysine salt mixtures with different drugs, including colour, clarity, pH and drug content were observed or measured before and after (up to 5 h) mixing at room temperature and under light protection. Results show that the association of Artrosilene® Fiale with different drugs does not cause, up to 5 h from mixing, any significant variation in the physicochemical parameters mentioned above. In conclusion, the results obtained demonstrated the physicochemical compatibility of ketoprofen lysine salt (Artrosilene® Fiale) with several drugs.

Keywords: Ketoprofen lysine salt; Pharmaceutical analysis; HPLC; Drugs interaction

1. Introduction

Ketoprofen lysine salt, an arylpropionic non-steroidal anti-inflammatory drug, is prescribed for the treatment of traumatic, orthopaedic and rheumatic disorders because of its anti-inflammatory and analgesic properties [1]. Since it is very often

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co-administered by intravenous infusion with other drugs, the possible interactions between the drugs used must be carefully evaluated. The combined therapy requires the knowledge of the mixture physicochemical compatibility, which can be achieved by determining the possible variations of the main physicochemical parameters, such as appearance (physical state and colour), pH and content of all active drugs of the mixture. Two mixed pharmaceutical products can be considered compatible when no significant variation of the physicochemical parameters of the mixture occurs. In fact, when two or more substances are mixed together, physical changes can occur, such as phase separation, formation of oil droplets and crystals [2]. Chemical incompatibility can take place after a variation of pH or, in extreme conditions, with a decrease in the drug content. The results of these modifications can cause a variation of therapeutic properties and undesirable side effects. Generally, drugs in an extemporary mixture are considered chemically incompatible when the content decrease of active drugs is more than 10% of their nominal value [3–7].

The term physical incompatibility or, more accurately, visual incompatibility, is used when the incompatibilities result in visible changes such as precipitation, turbidity or haziness, changes in colour or viscosity, effervescence, or formation of immiscible liquid layers. The term chemical incompatibility is used when interactions between drugs result in molecular changes or rearrangements to different chemical entities of the active compounds. Drugs may undergo a variety of chemical degradation pathways, such as hydrolysis, oxidation or reduction reactions, photodegradation, racemization or epimerization. The most important factors that influence the rate of drugs decomposition in drug delivery systems are solution pH and temperature. Drug concentration, light exposure and solution ion strength are also important factors. Most chemical incompatibilities are not visibly observable, therefore a useful technique to assure the drugs pharmaceutical integrity is to perform the quantitative determination of the drugs before and after mixing by means of very selective and sensitive analytical methods such as the chromatography [8–12].

In this study, an experimental protocol was designed to investigate the physicochemical compatibility of the associations between Artrosilene® Fiale injections, a marketed drug formulation for injection, and the following marketed drug products: Buscopan® Fiale (Boehringer Ingelheim Italia), Plasil® (Lepetit), Urbason® Solubile 20 (Aventis Pharma S.p.A.), Ranidil® 50 mg Soluzione Iniettabile (A. Menarini Industrie Sud s.r.l.), Ugurol® (Bayer), Rocefin® 2 (Roche), Glazidim™ 1 (Glaxo Wellcome), Unasyn® (Pfizer).

The following physicochemical parameters were evaluated immediately after mixing and after 1 and 5 h at room temperature and under light protection: colour, clarity, pH and drugs content.

2. Experimental

2.1. Chemicals

Acetonitrile (HPLC grade) and potassium dihydrogen phosphate (AnalaR grade) were supplied by Fluka Chemika–BioChemika (Buchs, Switzerland). Water (HPLC grade) was obtained by passage through the ELIX 3 and Milli-Q Academic water purification system (Millipore, Bedford, MA, USA). Ketoprofen lysine salt was supplied by Pharmacy Laboratory, Dompé. Other chemicals and reagents were of analytical grade.

The following marketed products were used for preparation of the mixtures:

- *Artrosilene® Fiale*: ketoprofen lysine salt 160 mg, citric acid, sodium hydroxide, water for injection; 2 ml
- *Buscopan® Fiale*: hyoscine-*N*-buthylbromide 0.02 g, sodium chloride 0.006 g water double distilled; 1 ml
- *Plasil®*: metoclopramide monohydrochloride 10 mg, sodium metabisulfite 2 mg; sodium chloride 14 mg, water for injection; 2 ml
- *Urbason® Solubile 20*: methylprednisolone hemisuccinate sodium salt 20.92 mg (equivalent to methylprednisolone 20 mg), sodium phosphate, sodium phosphate monobasic; solvent ampoule: water for injection 1 ml

- *Ranidil® 50 mg soluzione iniettabile*: ranitidine hydrochloride 55.8 mg (equivalent to ranitidine 50 mg), water for injection; 5 ml
- *Ugurol®*: tranexamic acid 0.5 g, methylparaben 5 mg, water for injection; 5 ml
- *Rocefin® 2*: ceftriaxone sodium salt 2.386 g (equivalent to ceftriaxone 2 g)
- *Glazidim™ 1*: ceftazidime pentahydrate 1.164 g (equivalent to ceftazidime 1 g), sodium carbonate anhydrous 116 mg; solvent: water for injection 10 ml (*)
- *Unasyn®*: sulbactam sodium salt 547 mg (equivalent to sulbactam 500 mg), ampicillin sodium salt 1063 mg (equivalent to ampicillin 1000 mg); solvent: water for injection 3.2 ml (*).

(*) Since the intravenous products were unavailable (hospital use only) on the market for both Glazidim™ 1 and Unasyn®, the marketed products for intramuscular injection were used in this experiment, being the composition of the powdered preparation for reconstitution the same as for the intravenous products. Nevertheless, the solvent and volume used for reconstitution were chosen to be the same as for the intravenous products.

2.2. Chromatographic system and conditions

HPLC analysis was carried out using a chromatographic system composed as follows: a Model 2690 pump, a Model 2487 UV–Vis detector (Waters, Milford, MA, USA). A model 7725i sample injector (Rheodyne, Cotati, CA, USA) equipped with a 20 μl loop was used. Chromatographic data management was automated using a software Millennium[32] (Waters, Milford, MA, USA). The analysis was performed on an analytical (250 × 4.6 mm i.d.) Luna C_{18} (5 μm particle size) column (Phenomenex, CA, USA). Separations were performed at room temperature. Mobile phases, sample dilution factors, volumes injected and wavelengths used for the separation of several drug associations, together with typical retention times, are reported in Table 1. The mobile phase was delivered at a flow-rate of 1.5 ml min^{-1}. The chosen chromatographic conditions were suitable to get a good resolution between the active drugs of the mixture, as shown in Table 1.

2.3. Sample preparation

The content of a single ampoule of Artrosilene® Fiale and one ampoule of each associated formulation were mixed and diluted to 50 ml with 0.9% NaCl aqueous solution (sterile and apyrogenic) into a glass flask. The obtained mixtures were protected from light by rolling up the stopped container with an aluminium foil, due to the well known photo-instability of ketoprofen, and maintained at room temperature. Lyophilised powder formulations were previously dissolved in the solvent enclosed in the marketed drug product and then mixed with ketoprofen lysine salt preparation. Before submitting for HPLC analysis, samples were appropriately diluted with Milli-Q water.

2.4. Colour, clarity and pH

The colour and clarity of the mixtures were evaluated by visual examination of the solution against a white background. The pH was measured by a Model PHM 92 pHmeter (Radiometer, Copenhagen). These parameters were evaluated before mixing, for each single formulation, immediately after mixing (time zero) and after 1 and 5 h from mixing.

3. Results and discussion

The characteristics of the preparations selected for the compatibility study with ketoprofen lysine salt injection are reported in Tables 2–4. Table 2 shows colour, clarity and pH of the solutions of pharmaceutical products tested in this study. The results of the direct mixing of Artrosilene® Fiale with the other pharmaceutical injectable preparations are reported in Table 3.

The single pharmaceutical products showed pH values ranging from 5.0 to 9.4; Artrosilene® Fiale formulation pH was equal to 6.9. As shown in Table 3, Artrosilene® Fiale resulted fully compatible with all drug products tested.

Table 1
Chromatographic conditions

Mixture	Mobile phase Na_2HPO_4 0.05 M (pH 7 with H_3PO_4)/CH_3CN	UV–Vis detection (nm)	Injected volume (μl)	Active molecule	Sample dilution factor	Retention time (min)
Artrosilene®	70/30	220	6	Ketoprofen lysine salt	250	3.5
Buscopan®	70/30	220		Hyoscine-*N*-buthylbromide		4.8
Artrosilene®	70/30	220	6	Ketoprofen lysine salt	250	3.5
Plasil®	70/30	220		Metoclopramide monohydrochloride		3.2
Artrosilene®	70/30	220	6	Ketoprofen lysine salt	250	3.5
Urbason®	70/30	220		Methylprednisolone		4.8
Artrosilene®	75/25	220	6	Ketoprofen lysine salt	250	6.2
Ranidil®	75/25	220		Ranitidine		2.3
Artrosilene®	70/30	254	6	Ketoprofen lysine salt	250	3.5
Ugurol®	98/2	220		Tranexamic acid		1.9
Artrosilene®	Gradient elution: up to 1 min 5% CH_3CN, then to 40% CH_3CN in 10 min	282	6	Ketoprofen lysine salt	5000	3.5
Rocefin® 2		282		Ceftriaxone		1.9
Artrosilene®	80/20	254	6	Ketoprofen lysine salt	5000	7.5
Glazidim™ 1	80/20	254		Ceftazidime		1.6
Artrosilene®	Gradient elution: up to 1 min 5% CH_3CN, then to 40% CH_3CN in 10 min	220	6	Ketoprofen lysine salt	2500	9.6
Unasyn®		220		Ampicillin sodium salt		6.9
				Sulbactam		3.7

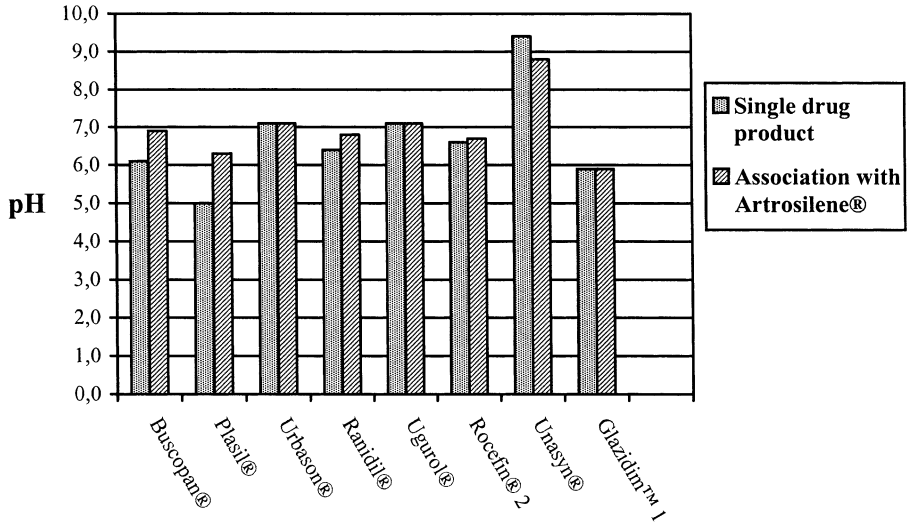

Fig. 1. Comparison between pH of the single formulations and of the mixtures.

Table 2
Physicochemical characteristics of pharmaceutical products tested

Commercial name	Colour and clarity of the solution	pH
Artrosilene® Fiale	Colourless, clear solution	6.9
Buscopan® Fiale	Colourless, clear solution	6.1
Plasil®	Colourless, clear solution	5.0
Urbason® solubile 20	Colourless, clear solution	7.1
Ranidil®	Colourless, clear solution	6.4
Ugurol®	Colourless, clear solution	7.1
Rocefin® 2	Light yellow, clear solution	6.6
Glazidim™ 1	Colourless, clear solution	5.9
Unasyn®	Colourless, clear solution	9.4

The colour, clarity and pH of all mentioned mixtures did not change significantly over 5 h after mixing.

In Fig. 1, the pH of the single formulations is compared with the pH obtained after mixing with Artrosilene® Fiale. It is noteworthy, that the pH values of the obtained mixtures are nearer to physiological pH than the single formulations, due to the presence of a buffer system in Artrosilene® Fiale formulation. The buffered Artrosilene® Fiale formulation ensures the maintenance of proper values of pH, more suitable for a safer intravenous administration.

The results of the HPLC analysis of the mixtures at time zero (immediately after mixing and gentle

Table 3
Colour, clarity and pH of Artrosilene® injection mixed with different pharmaceutical products

Mixtures	Volume (ml)	Colour and clarity			pH		
		$t=0$	$t=1$ h	$t=5$ h	$t=0$	$t=1$ h	$t=5$ h
Artrosilene® + Buscopan®	2+1/50	Colourless, clear solution	Unchanged	Unchanged	6.9	6.9	6.9
Artrosilene® + Plasil®	2+2/50	Colourless, clear solution	Unchanged	Unchanged	6.3	6.1	6.0
Artrosilene® + Urbason®	2+1/50	Colourless, clear solution	Unchanged	Unchanged	7.1	7.0	7.0
Artrosilene® + Ranidil®	2+5/50	Colourless, clear solution	Unchanged	Unchanged	6.8	6.8	6.8
Artrosilene® + Ugurol®	2+5/50	Colourless, clear solution	Unchanged	Unchanged	7.1	7.1	7.1
Artrosilene® + Rocefin® 2	2+40/50	Light yellow, clear solution	Unchanged	Unchanged	6.7	6.7	6.7
Artrosilene® + Glazidim™ 1	2+10/50	Colourless, clear solution	Unchanged	Unchanged	5.9	6.1	6.2
Artrosilene® + Unasyn®	2+3.2/50	Colourless, clear solution	Unchanged	Unchanged	8.8	8.7	8.6

Table 4
HPLC analysis of Artrosilene® injection mixed with different pharmaceutical products

Mixtures	Volume (ml)	Active drug	HPLC quantitative determination					
			$t = 0$		$t = 1$ h		$t = 5$ h	
			Concentration (mg/dose)	% Content vs. nominal value	Concentration (mg/dose)	% Content vs. nominal value	Concentration (mg/dose)	% Content vs. nominal value
Artrosilene® + Buscopan®	2+1/50	Ketoprofen lysine salt	160.6	100.4	161.0	100.6	160.1	100.0
		Hyoscine-*N*-buthyl-bromide	19.93	99.7	19.92	99.6	19.75	98.7
Artrosilene® + Plasil®	2+2/50	Ketoprofen lysine salt	161.1	100.7	162.4	101.5	162.8	101.7
		Metoclopramide monohydrochloride	9.90	99.0	9.98	99.8	10.10	101.0
Artrosilene® + Urbason®	2+1/50	Ketoprofen lysine salt	159.0	99.4	159.7	99.8	158.0	98.8
		Methylprednisolone	19.87	99.4	19.96	99.8	19.74	98.7
Artrosilene® + Ranidil®	2+5/50	Ketoprofen lysine salt	158.8	99.2	156.7	98.0	158.4	99.0
		Ranitidine	49.81	99.6	49.19	98.4	49.64	99.3
Artrosilene® + Ugurol®	2+5/50	Ketoprofen lysine salt	160.0	100.0	160.7	100.5	160.3	100.2
		Tranexamic acid	502.98	100.6	498.29	99.7	504.12	100.8
Artrosilene® + Rocefin® 2	2+40/50	Ketoprofen lysine salt	158.2	98.8	159.1	99.4	158.3	98.9
		Ceftriaxone	2010	100.6	2010	100.7	2020	101.1
Artrosilene® + Glazidim™ 1	2+10/50	Ketoprofen lysine salt	161.9	101.2	161.0	100.6	161.0	100.6
		Ceftazidime	1010	100.7	1000	99.5	1000	100.1
Artrosilene® + Unasyn®	2+3.2/50	Ketoprofen lysine salt	160.4	100.2	157.8	98.6	160.5	100.3
		Sulbactam	498.57	99.7	499.21	99.8	497.66	99.5
		Ampicillin sodium salt	1005.46	100.5	992.44	99.2	997.23	99.7

shaking), 1 and 5 h after mixing are reported in Table 4. The results confirmed the chemical compatibility between the formulations. In all studied mixtures the content of ketoprofen lysine salt and the associated active drug did not significantly change over the testing period. The content variation of all the active drugs remained well within 10% of their nominal values. Furthermore, there was no evidence of interaction/degradation products between the mixed drugs.

4. Conclusions

The possibility of combined therapy of Artrosilene® Fiale with various drugs (Buscopan® Fiale, Plasil®, Urbason® Solubile 20, Ranidil® 50 mg Soluzione Iniettabile, Ugurol®, Rocefin® 2, Glazidim™ 1, Unasyn®) requires the evaluation of physicochemical compatibility of the extemporary mixture to be performed. Therefore, on the basis of existing literatures [3–6] an experimental protocol was designed to investigate the compatibility between Artrosilene® Fiale and other drug formulations.

The observations and the measurements performed (colour, clarity, pH and content of active drugs) demonstrated the physicochemical compatibility of the extemporary mixtures of Artrosilene® Fiale with a number of steroidal anti-inflammatory, anti-hemorrhagic, anti-spastic, anti-ulcer, and antibacterial drugs.

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