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ANALYSIS

PHYSICAL COMPATIBILITY OF IBUPROFEN AND SELECTED PARENTERAL DRUGS DURING SIMULATED Y-SITE ADMINISTRATION

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Abstract: Intravenous ibuprofen (IBF) is indicated for short-term acute moderate pain and fever management. Limited data concerning the compatibility of intravenous IBF and other parenteral medications makes it inconvenient to use in polypharmacy-required patients. The simultaneous administration of two incompatible drugs is a health- or even life-threatening medical error. This study was performed to evaluate the physical compatibility of two intravenous IBF doses (600 mg/100 mL, 400 mg/100 mL) during Y-site administration with common parenteral medications. Eight infusion fluids, seven ready-to-use solutions for infusion, and thirty concentrates or powders for solutions for infusion were examined. All these drugs, if relevant, were reconstituted and diluted following the manufacturers' instructions to achieve concentrations found most commonly in clinical practice. Samples were prepared by mixing IBFs and selected drug product solutions at the 1 : 1 volume ratio. All samples underwent visual inspection and determination of pH and turbidity before combining with IBF and in time points (0, 30, 60, and 120 minutes) after simulated Y-site administration with IBF. In the case of propofol, which is an emulsion for infusion, lipid droplet size, zeta potential, and polydispersity index were also determined. The incompatibilities were observed for IBF combinations with amiodarone, ciprofloxacin, clemastine, gentamicin, vinpocetine, and calcium chloride.

Keywords: Y-site, intravenous administration, drug safety profile, turbidity, physical compatibility.

Ibuprofen (IBF) is a nonsteroidal anti-inflammatory drug known since the 1960s. It is used for treating pain, fever, and inflammation of different origins. It acts both centrally and peripherally to reduce pain and fever. The mechanism of its analgesic action is to prevent the sensitization of pain receptors at the site of injury. The anti-inflammatory properties resulting from the inhibition of the production of cyclooxygenase COX-1 and COX-2 enzymes may also contribute to promoting healing and resolution of pain (1). For years the use of IBF in the inpatient has been limited by the lack of a commercially available parenteral formulation. The lipophilic properties of the drug substance made it necessary to synthesize soluble salts (sodium and lysine salts) or use appropriate auxiliary substances (arginine) to obtain the intravenous dosage form (2, 3). The intravenous preparation of IBF containing arginine is indicated for the symptomatic treatment of short-term acute moderate pain and for the short-term symptomatic treatment of fever in situations where such administration is clinically warranted because other routes of administration cannot be used. Its dosing regimen in adults is 400 mg or 600 mg followed by repeated doses after 6 to 8 hours, depending on the patient's condition and response to treatment. The maximum total daily dose is 1200 mg, and the infusion time is 30 minutes. Intravenous administration of IBF can be an alternative to other nonsteroidal anti-inflammatory drugs or can be administered concomitantly with analgesics having another mechanism of action such as morphine, paracetamol, or metamizole sodium (4). The use of IBF is prevalent in multiple conditions, especially for peri- and postoperative pain management (5-7). Clinical trials showed that intravenous IBF may be a good alternative to intravenous paracetamol as part of multimodal postoperative analgesia in patients undergoing bariatric surgery or can be administered in combination with intravenous paracetamol at the fixed dose for the treatment

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of acute pain after orthopedic or plastic surgery (4, 8). It also effectively reduced fever in critically ill and non-critically ill patients (9). Both surgery and intensive care patients frequently require concomitant treatment with multiple intravenous medications, including intravenous anti-infective drugs, electrolytes, and infusion fluids. Simultaneous administration of intravenous drugs can be conducted only in situations when compatibility data are available. Such data are essential to ensure safe pharmacotherapy, especially in polypharmacy when co-administration of multiple drugs using Y-site is practically inevitable. Information concerning the compatibility of intravenous medications allows for avoiding the necessity of the placement of additional intravenous access catheters or careful planning of drug dosage schedules enabling their separate administration. Therefore, the compatibility studies of many drugs, including analgesics, have recently been widely conducted. Among non-opioid intravenous analgesics from the first step analgesic ladder, the compatibility of paracetamol (10-15), ketoprofen (15, 16), and ketorolac (11-17) with multiple other intravenous medications were determined. So far, investigations concerning the Y-site compatibility of intravenous IBF focused on IBF lysine used to close a clinically significant patent ductus arteriosus in premature infants (18, 19). In those studies, IBF lysine at the dose used in neonates was combined with three formulations of parenteral nutrition admixtures, one intravenous lipid admixture (18), and 34 intravenous medications at concentrations used clinically in such a population (19). Studies that undertake the problem of compatibility of intravenous IBF containing arginine as an auxiliary substance in adults are limited (10, 20). Foushee et al. determined the physical compatibility of hydrocortisone at a concentration of 1 mg/mL with thirteen intravenous medications, including IBF, showing their visual and turbidimetric compatibility when combined in equal volumes, simulating Y-site infusion (10). In another work, Foushee et al. showed the physical incompatibility of IBF at commercially available concentrations when combined with esmolol and labetalol in equal volumes (20). No other reports on the physical compatibility of intravenous IBF and the potential hazards of their co-infusion have been published. The limited compatibility data and the significant risk of incompatibility after combining IBF with other parenteral medications prompted us to conduct extensive research on this topic. In this study, we investigate the possibility of combining two commercially available intravenous IBF preparations with thirty-seven parenteral medications and eight infusion fluids commonly used in surgery and intensive care units.

MATERIAL AND METHODS

Material

Ibuprofen B. Braun 400 mg/100 mL (IBF 400) and Ibuprofen B. Braun 600 mg/100 mL (IBF 600) manufactured by B. Braun Melsungen AG were tested. Eight infusion fluids and sixty-one drug product preparations, resulting from the reconstitution of thirty-seven intravenous drugs selected for this study, are shown in Table 1. A summary of the infusion fluid preparations used, including their composition, is presented in Table 2.

Methods

Sample preparation

In order to achieve the concentrations found most commonly in clinical practice, all medications were reconstituted and diluted, if relevant, in accordance with the manufacturers' instructions. When more than one solution was recommended for reconstitution or dilution of the drug, two of them were selected, most often 0.9% sodium chloride solution (NS) and 5% glucose solution (G5) or NS and water for injections (W). Immediately after the preparation, initial pH, osmolality, turbidity, and additionally, in the case of propofol, parameters characteristic for lipid emulsion were determined. Then, all medications were mixed with IBF 400 and IBF 600 in a 1 : 1 ratio in 10 mL test tubes and incubated at room temperature for 2 hours to simulate Y-site administration. The 1 : 1 ratio of drug preparations was chosen, as previously described by many authors, to simulate the Y-site administration (10, 17, 19).

Visual inspection

Visual inspection was performed, according to European Pharmacopoeia requirements described in chapter 2.9.20, for each drug product solution prior to mixing and after combining with IBF preparations (21). Briefly, 5 mL of sample were transferred into clean, dry glass test tubes. Then, they were gently swirled to remove air bubbles and observed for 5 seconds against a black and white background by two independent observers. Any sign of visible particulates was noted.

Determination of physicochemical parameters of solutions for infusion

The pH was determined using a pH meter (Mettler Toledo Seven Compact pH/ion S220 pH meter, Mettler, Toledo, OH, USA), which was calibrated

Table 1. Parenteral drugs assessed for physical compatibility with ibuprofen.

Drug	Manufacturer	Lot	Symbol	Solvent	Concentration tested [mg/mL]
Infusion fluids					
5% Glucose	B. Braun Melsungen AG	21144404	G5	n. a.	50
10% Glucose	Fresenius Kabi Deutschland GmbH	L5QCDL30	G10	n. a.	100
Mannitol	Baxter Poland sp. z o.o.	21A05E4S	MAN	n. a.	150
Optilyte	Fresenius Kabi Deutschland GmbH	15PFA750	OPT	n. a.	see Table 2
Plasmalyte	Baxter Poland sp. z o.o.	21A16E9Z	PLA	n. a.	see Table 2
Ringer's solution	Fresenius Kabi Deutschland GmbH	15QCC810	RIN	n. a.	see Table 2
Ringer's solution with lactate	Fresenius Kabi Deutschland GmbH	15QCE040	RIL	n. a.	see Table 2
0.9% Sodium chlorate	B. Braun Melsungen AG	19381450	NS	n. a.	9
Ready-to-use solution for infusion					
Ciprofloxacin	Polpharma S.A.	1030220	CPX	n. a.	2
Fluconazole	Pfizer	B5029036	FLZ	n. a.	2
Gentamycin(sulfate)	B. Braun Melsungen AG	19373408	GNT	n. a.	3
Metronidazole	Polpharma S.A.	2010920	MTZ	n. a.	5
Paracetamol	B. Braun Melsungen AG	19402402	PAR	n. a.	10
Piracetam	Polpharma S.A.	510321	PIR	n. a.	200
Propofol	B. Braun Melsungen AG	3547221	PRO	n. a.	10
Concentrates for solution for infusion					
Amiodarone (hydrochloride)	KRKA	A71357	AMI	G5	1.2
Calcium chloride	Polfa Warszawa S.A.	60617	CAL A	NS	50
			CAL B	G5	50
Clemastine (fumarate)	Polfa Warszawa S.A.	07ANO220	CLE A	NS	0.2
			CLE B	G5	0.2
Clindamycin (phosphate)	Sandoz GmbH	KH9501	CLI A	NS	11.1
			CLI B	G5	11.1

Table 1. Parenteral drugs assessed for physical compatibility with ibuprofen (cont.).

Drug	Manufacturer	Lot	Symbol	Solvent	Concentration tested [mg/mL]
Kalium chlorate	Polfa Warszawa S.A.	13DF0517	KAL A	NS	3 (K^+ 0.04 mmol/L)
			KAL B	G5	3 (K^+ 0.04 mmol/L)
Magnesium (sulfate)	Polpharma S.A.	50217	MAG A	NS	1.8
			MAG B	G5	1.8
Metamizole sodium	Polpharma S.A.	30520	MTM A	NS	45.5
			MTM B	G5	45.5
Midanium	Polfa Warszawa S.A.	01DS0118	MID A	NS	0.01
			MID B	G5	0.01
Morphine (sulfate)	Polfa Warszawa S.A.	01DR0618	MOR A	NS	2
			MOR B	W	2
Ondansetron (hydrochloride)	Fresenius Kabi Deutschland GmbH	18S028001	OND A	NS	0.15
			OND B	G5	0.15
Sodium bicarbonate	Polpharma S.A.	50121	SBC	G5	42
Sulfamethoxazole + Trimethoprim	Polfa Warszawa S.A.	05CE1019	SMT A	NS	3.2 + 0.6
			SMT B	G5	3.2 + 0.6
Theophylline	Biofarm sp. z o.o.	2100864	TPL A	NS	1.8
			TPL B	NS	0.8
Vinpocetine	Gedeon Richter Plc.	A93002	VIN A	NS	0.1
			VIN B	G5	0.1
Powders for solution for infusion					
Aciclovir (sodium salt)	PharmaSwiss	810031	ACV	NS	5
Amocillin + Clavulanic acid	Polfa Tarchomin S.A.	2021220	AMC A	NS	8.3 + 1.7
			AMC B	W	8.3 + 1.7
Ampicillin (sodium salt)	Polfa Tarchomin S.A.	3010920	AMP	W	10
Cefazolin (sodium salt)	Sanofi-Aventis France	KA8559	CFL	NS	20

Table 1. Parenteral drugs assessed for physical compatibility with ibuprofen (cont.).

Drug	Manufacturer	Lot	Symbol	Solvent	Concentration tested [mg/mL]
Cefotaxime (sodium salt)	Polpharma S.A.	26011119A	CFT A	NS	20
			CFT B	G5	20
Ceftriaxone (sodium salt)	Polfa Tarchomin S.A.	1031019	CFR A	NS	20
			CFR B	G5	20
Ceftazidime	Polpharma S.A.	5060220A	CFZ A	NS	20
			CFZ B	G5	20
Cefuroxime (sodium salt)	Polpharma S.A.	205109A	CFX A	NS	23.1
			CFX B	G5	23.1
Cloxacillin (sodium salt)	Polfa Tarchomin S.A.	2011020	CLX A	NS	4
			CLX B	G5	4
Hydrocortisone (sodium hemisuccinate)	PharmaSwiss Česká republika s.r.o.	905091	HCS A	NS	1
			HCS B	G5	1
Imipenem + cilastatin	Ranbaxy	AB49353	IMC	NS	5 + 5
Meropenem	Fresenius Kabi Deutschland GmbH	MPL1098	MER A	NS	10
			MER B	G5	10
Omeprazole	Zentiva	2300321	OMZ A	NS	0.4
			OMZ B	G5	0.4
Pantoprazole	Takeda GmbH	483758	PNZ A	NS	0.4
			PNZ B	G5	0.4
Valproic acid (sodium salt)	Sanofi-Aventis France	A090641	VPA A	NS	0.8
			VPA B	G5	0.8
Vancomycin (hydrochloride)	Sanofi-Aventis France	KU6713	VMC A	NS	4.6
			VMC B	G5	4.6

NS — normal saline; G — 5% glucose solution; W — water for injection; n. a. — not applicable

Table 2. Composition of tested infusion solutions.

Component	Concentration [mmol/L]							
	0.9% sodium chloride solution (NS)	5% glucose solution (G5)	10% glucose solution (G10)	Optilyte (OPT)	Plasmalyte (PLA)	Ringer's solution (RIN)	Ringer's solution with lactate (RIL)	20% solution of mannitol (MAN)
Na^+	154	0	0	141	140	147.2	130.5	0
Cl^-	154	0	0	109	98	155.7	109.6	0
K+	0	0	0	5	5	4	4	0
Ca^{2+}	0	0	0	2	0	2.3	1.4	0
Mg^{2+}	0	0	0	1	1.5	0	0	0
Acetate	0	0	0	34	27	0	0	0
Citrate	0	0	0	3	0	0	0	0
Gluconate	0	0	0	0	23	0	0	0
Lactate	0	0	0	0	0	0	27.7	0
Glucose	0	278 (50 g/L)	556 (100 g/L)	0	0	0	0	0
Mannitol	0	0	0	0	0	0	0	1097.9 (200 g/L)

at three points against standard buffers at pH 4.0, 7.0, and 10.0. The pH of all samples was measured at the temperature of 24 ± 1°C. The osmolarity was determined by the cryoscopy method using an 800CL TridentMed® osmometer (Trident Med s.c., Warsaw, Poland). The pH and osmolarity were determined for each drug product solution prior to mixing with IBF and immediately after combining with IBF. The turbidity was determined using a Hach TU5200 turbidimeter. Before the measurements, the apparatus was calibrated according to the manufacturer's instructions against the formazin turbidity standards 20 NTU and 600 NTU and verified using the 10 NTU standard. In order to exclude the presence of insoluble particles or precipitate, especially in the case of powders for solution for infusion, each solution after reconstitution and prior to mixing with IBF was filtered using a 0.2 µm pore size, polytetrafluoroethylene filter. The control solutions for turbidity analysis were prepared by diluting the tested drug solution in NA or W in the volume ratio 1 : 1. The turbidity was determined for each mixture immediately after preparation (t = 0 minutes) and at 30, 60, and 120 minutes after preparation. All the measurements were performed in triplicate, and the results were expressed as average ± standard deviation. To consider the medication for infusion to be compatible with IBF, the turbidity of combined drugs cannot exceed the literature acceptance limit of +0.5 NTU in relation to the initial values observed for components of the mixture diluted 1 : 1 with the solvent used for reconstitution of the drug product.

Determination of physicochemical parameters characteristic for emulsion for infusion

The lipid emulsion particle size and zeta potential of propofol emulsion for infusion and tested combination of this medication with IBF 400 and IBF 600 were determined by dynamic light scattering and laser Doppler velocimetry methods using a Zetasizer Nano ZS (Malvern Instruments, Malvern, United Kingdom). The measurements were

performed at the temperature of 25°C on diluted 1 : 10 with water for injection samples. The homogeneity of the samples was determined by the polydispersity index (PDI). The results are presented as intensity-weighted mean droplet diameter (MDD) and zeta potential (ZP). All the measurements were performed in triplicate, and the results were expressed as average ± standard deviation. To consider the emulsion for injection to be compatible with IBF, the MDD cannot exceed the US pharmacopeial limit of 500 nm set for the method I for the determination of the mean droplet size of injectable lipid emulsions (22).

RESULTS

All tested medications prior to combining with IBF met the requirements for intravenous administration. Solutions for infusion were clear, transparent, and colorless, with no precipitate detected by the unaided human eye. The PRO emulsion for infusion was milky-white with no sign of emulsion destabilization. The pH and osmolality of IBF 400 and IBF 600 were 7.29 ± 0.01 and 7.34 ± 0.01, and 331 ± 1 mOsm/kg and 353 ± 1 mOsm/kg, respectively. The studied drugs differed in pH values, ranging from 3.39 ± 0.00 for VMC A to 10.57 ± 0.01 for ACV. The highest osmolality of tested drugs was observed for CLE B (1599 ± 1 mOsm/kg) and for PIR (1599 ± 5 mOsm/kg), the lowest for MOR B. The turbidity of IBF 400 and IBF 600 was 0.103 ± 0.007 NTU and 0.193 ± 0.005 NTU, respectively. Excepting IMC, which turbidity was 1.550 ± 0.230 NTU, none of the chosen drug product solutions were characterized by turbidity higher than 1 NTU, and they were in the range of 0.064 ± 0.007 (for FLZ) to 0.726 ± 0.030 NTU (for CFX B). Results are shown in Table 3.

Table 3. Physicochemical parameters of studied drug products solutions and results of their compatibility with ibuprofen.

Sample	pH ± SD	Osmolarity ± SD [mOsm/kg]	Turbidity ± SD [NTU]	Compatibility results	
				With IBF 400	With IBF 600
Ibuprofen					
IBF 400	7.29 ± 0.01	331 ± 1	0.103 ± 0.007	-	-
IBF 600	7.34 ± 0.01	353 ± 1	0.193 ± 0.005	-	-
Infusion fluids					
G5	4.84 ± 0.02	290 ± 0	0.157 ± 0.005	Compatible	Compatible
G10	4.97 ± 0.01	604 ± 1	0.140 ± 0.002	Compatible	Compatible
MAN	7.12 ± 0.01	941 ± 1	0.485 ± 0.013	Compatible	Compatible
OPT	7.02 ± 0.01	262 ± 2	0.082 ± 0.013	Compatible	Compatible
PLA	7.21 ± 0.01	265 ± 2	0.174 ± 0.017	Compatible	Compatible
RIL	6.60 ± 0.01	248 ± 1	0.092 ± 0.013	Compatible	Compatible
RIN	6.30 ± 0.01	273 ± 0	0.128 ± 0.024	Compatible	Compatible
NS	6.66 ± 0.03	287 ± 2	0.083 ± 0.009	Compatible	Compatible
Ready-to-use solution for infusion					
CPX	4.10 ± 0.02	293 ± 3	0.160 ± 0.014	Incompatible	Incompatible
FLZ	6.66 ± 0.02	289 ± 1	0.064 ± 0.007	Compatible	Compatible
GNT	4.52 ± 0.01	288 ± 1	0.146 ± 0.008	Incompatible	Incompatible
MTZ	5.81 ± 0.02	276 ± 2	0.114 ± 0.003	Compatible	Compatible
PAR	5.31 ± 0.01	296 ± 1	0.165 ± 0.007	Compatible	Compatible
PIR	5.69 ± 0.01	1599 ± 5	0.131 ± 0.018	Compatible	Compatible
PRO	7.49 ± 0.02	330 ± 2	n. a.	Compatible	Compatible
Concentrates for solution for infusion					
AMI	3.85 ± 0.01	288 ± 2	0.241 ± 0.038	Incompatible	Incompatible
CAL A	6.28 ± 0.01	722 ± 2	0.300 ± 0.012	Compatible	Incompatible
CAL B	5.43 ± 0.01	667 ± 1	0.129 ± 0.009	Compatible	Incompatible
CLE A	5.40 ± 0.01	1497 ± 1	0.077 ± 0.010	Incompatible	Incompatible
CLE B	5.90 ± 0.01	1599 ± 1	0.204 ± 0.012	Incompatible	Incompatible

Table 3. Physicochemical parameters of studied drug products solutions and results of their compatibility with ibuprofen. (cont.).

Sample	pH ± SD	Osmolarity ± SD [mOsm/kg]	Turbidity ± SD [NTU]	Compatibility results	
				With IBF 400	With IBF 600
CLI A	6.48 ± 0.01	316 ± 3	0.141 ± 0.016	Compatible	Compatible
CLI B	6.72 ± 0.01	329 ± 1	0.211 ± 0.011	Compatible	Compatible
KAL A	6.72 ± 0.01	341 ± 3	0.605 ± 0.055	Compatible	Compatible
KAL B	5.99 ± 0.01	355 ± 2	0.289 ± 0.019	Compatible	Compatible
MAG A	6.37 ± 0.02	331 ± 1	0.342 ± 0.022	Compatible	Compatible
MAG B	6.18 ± 0.01	342 ± 2	0.166 ± 0.017	Compatible	Compatible
MTM A	6.40 ± 0.01	543 ± 2	0,257 ± 0.031	Compatible	Compatible
MTM B	6.38 ± 0.01	559 ± 1	0.299 ± 0.023	Compatible	Compatible
MID A	5.11 ± 0.01	283 ± 2	0.228 ± 0.010	Compatible	Compatible
MID B	4.61 ± 0.01	291 ± 1	0.170 ± 0.025	Compatible	Compatible
MOR A	5.87 ± 0.01	288 ± 1	0.241 ± 0.038	Compatible	Compatible
MOR B	5.66 ± 0.01	34 ± 1	0.164 ± 0.013	Compatible	Compatible
OND A	4.85 ± 0.01	289 ± 1	0.276 ± 0.007	Compatible	Compatible
OND B	4.88 ± 0.01	294 ± 1	0.101 ± 0.007	Compatible	Compatible
SBC	8.06 ± 0.00	1022 ± 1	0.774 ± 0.025	Compatible	Compatible
SMT A	9.50 ± 0.00	655 ± 1	0.337 ± 0.009	Compatible	Compatible
SMT B	9.28 ± 0.01	626 ± 0	0.146 ± 0.024	Compatible	Compatible
TPL A	9.03 ± 0.01	304 ± 1	0.358 ± 0.011	Compatible	Compatible
TPL B	8.99 ± 0.01	294 ± 1	0.208 ± 0.013	Compatible	Compatible
VIN A	3.46 ± 0.00	291 ± 1	0.160 ± 0.014	Incompatible	Incompatible
VIN B	3.73 ± 0.01	299 ± 2	0.177 ± 0.003	Incompatible	Incompatible
Powders for solution for infusion					
ACV	10.57 ± 0.01	318 ± 2	0.442 ± 0.024	Compatible	Compatible
AMC A	8.89 ± 0.00	299 ± 1	0.107 ± 0.010	Compatible	Compatible
AMC B	9.07 ± 0.01	62 ± 2	0.177 ± 0.012	Compatible	Compatible
AMP	9.24 ± 0.00	70 ± 5	0.178 ± 0.006	Compatible	Compatible
CFL	5.02 ± 0.01	326 ± 1	0.355 ± 0.015	Compatible	Compatible
CFR A	6.25 ± 0.01	308 ± 0	0.554 ± 0.008	Compatible	Compatible
CFR B	6.43 ± 0.01	319 ± 1	0.160 ± 0.009	Compatible	Compatible
CFT A	5.35 ± 0.01	328 ± 1	0.272 ± 0.018	Compatible	Compatible
CFT B	5.42 ± 0.01	337 ± 0	0.277 ± 0.016	Compatible	Compatible
CFX A	7.23 ± 0.01	316 ± 3	0.512 ± 0.007	Compatible	Compatible
CFX B	7.28 ± 0.00	323 ± 2	0.726 ± 0.030	Compatible	Compatible
CFZ A	6.93 ± 0.01	336 ± 1	0.133 ± 0.007	Compatible	Compatible
CFZ B	7.01 ± 0.00	349 ± 2	0.289 ± 0.016	Compatible	Compatible
CLX A	5.68 ± 0.00	291 ± 4	0.171 ± 0.033	Compatible	Compatible
CLX B	5.04 ± 0.01	294 ± 1	0.100 ± 0.003	Compatible	Compatible
HCS A	7.38 ± 0.01	286 ± 0	0.254 ± 0.014	Compatible	Compatible
HCS B	7.69 ± 0.02	290 ± 0	0.217 ± 0.016	Compatible	Compatible
IMC	7.54 ± 0.01	326 ± 2	1.550 ± 0.230	Compatible	Compatible
MER A	7.88 ± 0.00	327 ± 1	0.470 ± 0.004	Compatible	Compatible
MER B	8.10 ± 0.00	331 ± 1	0.425 ± 0.023	Compatible	Compatible
OMZ A	9.92 ± 0.02	286 ± 3	0.109 ± 0.004	Compatible	Compatible

Table 3. Physicochemical parameters of studied drug products solutions and results of their compatibility with ibuprofen. (cont.).

Sample	pH ± SD	Osmolarity ± SD [mOsm/kg]	Turbidity ± SD [NTU]	Compatibility results	
				With IBF 400	With IBF 600
OMZ B	9.54 ± 0.01	294 ± 2	0.166 ± 0.006	Compatible	Compatible
PNZ A	9.36 ± 0.00	281 ± 2	0.240 ± 0.011	Compatible	Compatible
PNZ B	8.90 ± 0.02	64 ± 1	0.294 ± 0.020	Compatible	Compatible
VPA A	6.58 ± 0.01	287 ± 0	0.203 ± 0.007	Compatible	Compatible
VPA B	6.50 ± 0.01	296 ± 1	0.080 ± 0.003	Compatible	Compatible
VMC A	3.39 ± 0.00	294 ± 1	0.330 ± 0.025	Compatible	Compatible
VMC B	3.41 ± 0.00	260 ± 3	0.254 ± 0.034	Compatible	Compatible

NS ─ normal saline; G5 ─ 5% glucose solution; W ─ water for injection; n. a. ─ not applicable

PRO, an emulsion for infusion, was characterized by the MDD, ZP, and PDI equal to 213.1 nm, -3.2 mV, and 0.163, respectively. The visual appearance, pH, osmolarity, and turbidity were measured for each mixture immediately after preparation and in predetermined intervals. Due to the inability to perform turbidity assay in lipid emulsion preparations, in the case of PRO, instead of turbidity, the MDD and ZP were determined. Among all tested mixtures, twelve immediately after mixing became opaque or formed precipitate visible with the unaided eye, two exceeded the assumed level of acceptable turbidity despite the lack of visual signs of this phenomenon, and two were within turbidity limits but precipitated in time. The results of the turbidity and pH measurements of tested mixtures are shown in Table 4 and Table 5, respectively.

Table 4. Turbidity analysis of incompatible combinations of parenteral drugs and ibuprofen.

Sample	Control solution[C]	Time after mixing with IBF 400 [min]			
		0 (immediately)	30	60	120
AMI	0.180 ± 0.018	1.400 ± 0.020	2.633 ± 0.046	3.567 ± 0.015	5.193 ± 0.012
CPX	0.098 ± 0.009	686.667 ± 21.362*	996.000 ± 1.000*	855.333 ± 11.930*	629.000 ± 3.536*
CLE A	0.081 ± 0.006	375.000 ± 6.000*	199.333 ± 2.309*	204.333 ± 0.577*	125.667 ± 0.577*
CLE B	0.147 ± 0.008	465.667 ± 16.258*	264.333 ± 0.577*	192.000 ± 1.000*	160.667 ± 0.577*
GNT	0.112 ± 0.005	> 1000[R]*	550.667 ± 2.517*	424.667 ± 26.633*	296.000 ± 14.719*
VIN A	0.122 ± 0.004	> 1000[R]*	586.000 ± 9.849*	426.000 ± 4.583*	299.667 ± 9.192*
VIN B	0.130 ± 0.006	> 1000 [R]*	716.667± 28.885*	556.333± 12.858*	442.000 ± 11.790*
Sample	Control solution[C]	Time after mixing with IBF 600 [min]			
		0 (immediately)	30	60	120
AMI	0.180 ± 0.016	2.250 ± 0.030	5.780 ± 0.040	7.570 ± 0.030	9.590 ± 0.030
CAL A	0.160 ± 0.007	0.337 ± 0.016	5.980 ± 0.928*	38.267 ± 0.380*	404.333 ± 22.630*
CAL B	0.106 ± 0.008	0.278 ± 0.012	2.957 ± 0.367*	35.767 ± 0.379*	216.333 ± 24.440*
CPX	0.098 ± 0.009	606.000 ± 12.288*	870.333 ± 14.572*	879.667 ± 33.486*	793.667 ± 14.849*
CLE A	0.081 ± 0.006	440.000 ± 6.000*	273.000 ± 1.000*	197.667 ± 0.577*	167.667 ± 0.577*
CLE B	0.147 ± 0.008	556.000 ± 5.000*	364.000 ± 1.000*	271.333 ± 0.577*	218.000 ± 0.000*
GNT	0.112 ± 0.005	858.667 ± 7.024*	950.000 ± 6.557*	813.000 ± 20.000*	566.333 ± 11.060*
VIN A	0.122 ± 0.004	> 1000[R]*	633.667 ± 25.423*	483.000 ± 10.440*	364.000 ± 9.899*
VIN B	0.130 ± 0.006	> 1000[R]*	743.667 ± 21.455*	563.667 ±15.535*	436.333 ± 12.097*

[C] – Control solution is the tested drug solution diluted in NS (AMI in W) in ratio 1 : 1, * Turbidity observed with the unaided eye, [R] – Above the range of turbidimeter

Table 5. pH measurement results of incompatible combinations of IBF with parenteral drugs

Sample	pH				
	Before mixing with IBF	with IBF 400		with IBF 600	
		2 h after mixing	Difference	2 h after mixing	Difference
AMI	3.85 ± 0.01	6.88 ± 0.01	+3.03	7.08 ± 0.01	+3.23
CAL A	6.28 ± 0.01	6.96 ± 0.01	+0.68	7.08 ± 0.01	+0.80
CAL B	5.43 ± 0.01	6.94 ± 0.01	+1.51	6.97 ± 0.00	+1.54
CPX	4.10 ± 0.02	5.80 ± 0.00	+1.70	6.06 ± 0.00	+1.96
CLE A	5.40 ± 0.01	6.75 ± 0.01	+1.35	7.00 ± 0.01	+1.60
CLE B	5.90 ± 0.01	6.79 ± 0.01	+0.89	6.94 ± 0.01	+1.04
GNT	4.52 ± 0.01	5.84 ± 0.00	+1.32	6.17 ± 0.01	+1.65
VIN A	3.46 ± 0.00	5.93 ± 0.01	+2.47	5.97 ± 0.01	+2.51
VIN B	3.73 ± 0.01	6.18 ± 0.00	+2.45	6.21 ± 0.01	+2.48

For some combinations, the measure values of turbidity were above the turbidimeter range. This was observed for IBF 400 mixtures with GNT, VIN A, and VIN B, as well as for IBF 600 combinations with VIN A and VIN B. The visible turbidity observed immediately after preparation for IBF 400 and IBF 600 combined with CPX, CLE A, CLE B, GNT, VIN A, and VIN B was maintained at the following time points. The mixtures of IBF 600 with CAL A and CAL B had acceptable turbidity of 0.337 ± 0.016 NTU and 0.278 ± 0.012 NTU, respectively, immediately after mixing. In this case, the turbidity was not visible to the unaided eye immediately after mixing. However, the visual changes appeared after 30 minutes, and precipitate formation increased in time until the end of the study. In the case of AMI combined with either IBF 400 or IBF 600, despite exceeding the assumed level of acceptable turbidity determined using the turbidimeter, no visible changes were observed throughout the entire test period. Combining PRO with IBF in tested concentrations did not decrease the lipid emulsion stability (Figure 1).

The MDD of IBF 400 and IBF 600 combinations with PRO throughout the entire study period did not exceed 214.7 nm and 210.4 nm, respectively. PDI of studied IBF doses was below 0.148. The ZP, which is the potential difference between the dispersion medium and the interfacial double layer of the dispersed particle, decreased with the increased concentration of IBF. Immediately after preparation, the ZP of samples containing IBF 400 and PRO was equal to -19.5 mV, whereas the mixture of IBF 600 and PRO was equal to -24.9 mV. During the storage, the absolute value of ZP for IBF 400 and PRO as well as IBF 600 and PRO increased to -24.3 mV and -27.9 mV, respectively. Simultaneously, the absolute value of ZP for the control sample (PRO+NS) was lower and equal to -14.5 ± 0.1 mV.

DISCUSSION

To consider drug product solutions to be physically compatible when administered using Y-site with another infusion drug, the mixture of drugs combined in appropriate ratios cannot produce any particulate matter, color change, or increased turbidity, and additionally, in the case of emulsion for infusion, affect the lipid emulsion stability manifested with increased droplet size. All drugs were reconstituted along with the manufacturers' instructions. To maximize the application aspect of this research enabling the direct use of our results in clinical practice mediation for which the summary of product characteristics provides the possibility of reconstitution using different infusion fluids, two solutions (A and B) were prepared. Intravenous infusion of precipitate particles depending on their size and amount can lead to severe embolic events and death. For this reason, turbidity (in the case of solutions) and MDD (in the case of emulsions) are the main factors in determining compatibility. Other determinants such as pH, osmolality, and zeta potential are auxiliary parameters allowing identification of the causes of incompatibilities. The visual inspection aims to detect unintended contamination of extraneous particles other than gas bubbles in intravenous solutions (injections/infusions). Although it is a simple procedure that allows evaluating the quality of parenteral drugs, it possesses several limitations. First of all, the detection of contamination depends on the subjective assessment of the observer and their personal detection abilities. There is no specific size cut-off value for particles being visible to

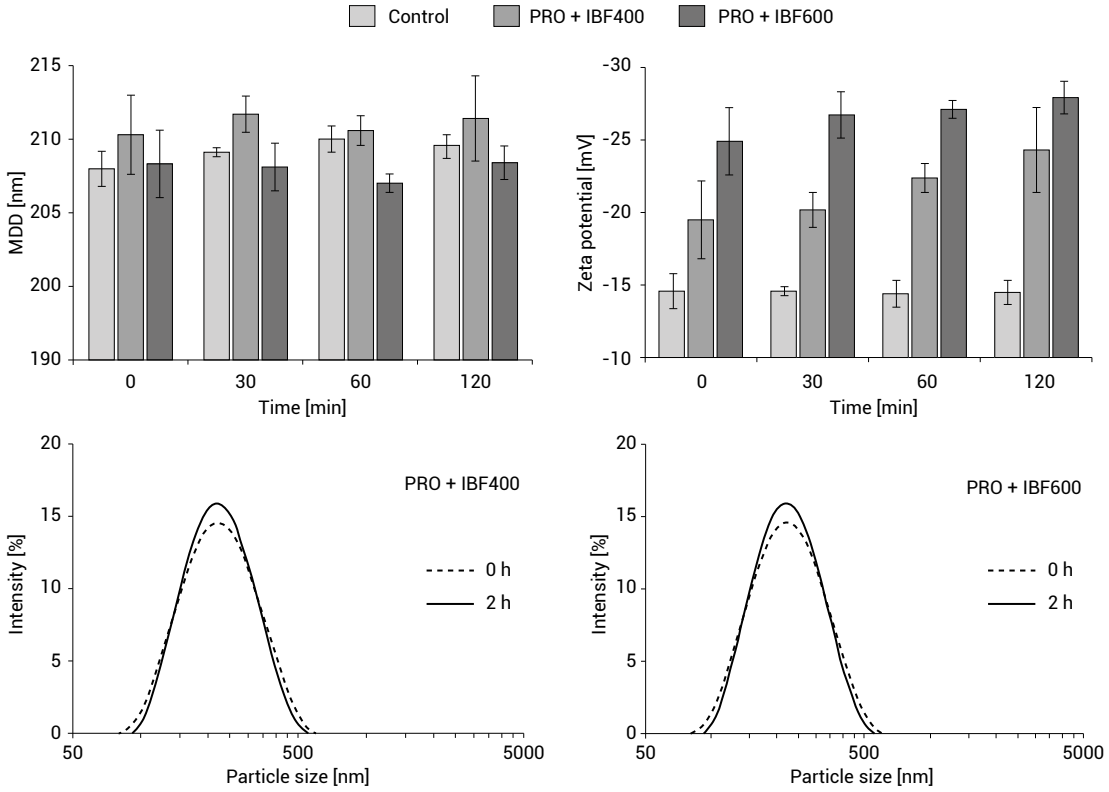

Figure 1. Combination of IBF and PRO: lipid emulsion particle size, particle distribution, and zeta potential (MDD: mean droplet diameter; Control: PRO+NS 1 : 1).

the human eye; thus, this method is burdened with little confidence in the results obtained. In practice, it is based on a statistical process that can be affected by morphology and the number of particles and properties of solution being under investigation, their viscosity, rheology, and opalescence. The type of test tube, its material, shape, and size are other factors that may change the ability of the observer for particle detection (23). For this reason in this study, along with visual inspection, the turbidity and MDD measurements were performed.

Among all tested mediations, IBF in both tested concentrations proved to be incompatible with AMI, CPX, CLE, GNT, and VIN. A summary of the compatibility results is presented in Table 3. The incompatibility of IBF 400 and IBF 600 with CPX, CLE, GNT, and VIN was unquestionable due to the immediate appearance of opaque and precipitate formation visible with the unaided eye. In the case of IBF and AMI mixtures, the turbidity significantly exceeded the literature acceptance limit of +0.5 NTU (24-26), and after 2 h of storage, it reached the value of 5.193 ± 0.012 NTU or 9.590 ± 0.030 NTU depending on the concentration of IBF solutions. However, the particles of the precipitate formed were of very small size, and therefore the turbidity was not visually observed. Moreover, IBF 600 solution was also incompatible with CAL solutions, and such incompatibility was not found for IBF 400. Although the precipitate was observed only in the mixture with a higher concentration of IBF, the simultaneous administration of CAL and IBF 400 should also be avoided. All incompatible solutions had a lower pH (Table 5) than the IBF 400 and IBF 600 solutions which pH was about 7.3 (Table 3). However, the pH of the drug product solution was not the only factor that contributed to the incompatibility of the tested preparations. Low pH of VMC (VMC A: 3.46; VMC B: 3.73), MID B (4.61), or OND (4.85–4.88) solutions did not result in their incompatibility with IBF revealed as increased turbidity of the samples. In the case of the IBF mixtures with CLE, their incompatibility results presumably from the coexistence of two factors: low pH and the presence of excipients in the CLE preparation. The concentration of CLE in the tested solution was only 0.2 mg/mL, and the osmolality of the solutions was about 1500-1600 mOsm/kg, which means that the concentration of one or more of the declared auxiliary substances: sorbitol, ethanol, propylene glycol, sodium citrate was high and affected the osmolarity of the solution. Most of the infusion fluids were

characterized by osmolality similar to isotonic solutions of 262-355 mOsm/kg, and lower osmolality was observed only for solutions prepared using water for injection as a diluent (AMC B, MOR B, and PNZ B). The high osmolality of the drug products solution itself did not affect compatibility with IBF 400 and IBF 600. Besides CLE, high osmolality was also determined for CAL (677-722 mOsm/kg), G10 (604 mOsm/kg), MAN (941 mOsm/kg), MTM (543-559 mOsm/kg), PIR (1599 mOsm/kg), SBC (1022 mOsm/kg) and SMT (626-655 mOsm/kg). Among the above-listed infusion solutions, only CAL was proved to be incompatible.

Lipid emulsions may interact with other drugs, especially those containing electrolytes or glucose (27). These interactions can cause aggregation of lipid droplets, and too large lipid droplets lead to the embolization of blood vessels. In extreme cases, destabilization of the emulsion system may occur. Interestingly, the mixture of IBF with PRO led to increased ZP value with no significant affection on lipid emulsion droplet size (MDD). The high absolute value of ZP indicates the stability of the dispersed system. Therefore, the observed lower ZP value in samples containing combinations of PRO with IBF 400 and IBF 600 in contrast to the control sample, as well as the lower ZP value observed with increasing concentration of IBF, indicate the stabilizing effect of IBF on the oil-in-water system of a pharmaceutical preparation of propofol.

Due to the very little information on the compatibility of ibuprofen infusion as an arginine salt, only one of our observations can be compared with the results of studies by other authors. Similar to studies by Foushee et al. IBF 400 was shown to be compatible with HCS (10). Analysis of literature data concerning drugs found to be incompatible with IBF shows that those drugs reveal incompatibility also with other intravenous medications. CPX was observed to form a gross precipitate and an increase in turbidity at least 30 minutes after admixture with meropenem/vaborbactam, fosfomycin, and cloxacillin sodium (28-30). It was also chemically incompatible with hydrocortisone sodium succinate (31). In combination with pemetrexed disodium, CPX underwent slight color darkening that occurred over 4 hours, whereas GNT formed a gross white precipitate immediately after mixing (32). GNT was proved to be incompatible with propofol when combined in a 1 : 1 ratio (33). CAL and AMI should also not be administered using Y-site when combined with plazomicin (34).

Our results showed that the physical incompatibility of two drugs co-administered via Y-site is difficult to predict based on simple physicochemical parameters such as pH or osmolality, and its observation is not always possible with the unaided eye. The observed changes in the turbidity of the solution or particle size of the lipid emulsion may be the result of both the chemical structure of the drug substance, the physicochemical properties of the preparation, its acid-base character, the concentration of the active substance, as well as the presence and concentration of auxiliary substances. The obtained results clearly confirm that the combined administration of intravenous drugs using Y-site can take place only in situations when available data about the compatibility of drug product preparations takes into account all factors that may affect it.

CONCLUSIONS

The problem of drug incompatibility in the case of intravenous drugs is extremely important because the concomitant administration of incompatible drugs may lead to disruptions in the treatment process (lack of the intended pharmacological effect) or lead to complications as a result of the infusion of particles with large size which can cause the blood vessels embolization. IBF in both tested concentrations proved to be physically compatible with all tested infusion fluids and twenty-nine parenteral medications when simulated Y-site administration. The incompatibilities manifested by visible precipitate formation or turbidity changes were observed for IBF mixtures with amiodarone, ciprofloxacin, clemastine, gentamicin, vinpocetine, and calcium chloride.

Limitations

- The results of ibuprofen compatibility with selected drug substances in preparations other than those listed in Table 1 may differ from the results presented in the work due to the different qualitative and quantitative compositions of the excipients and the different pH of these products.
- This article uses the methodology adopted by many investigators and considers only one ratio between drugs administered via the Y-site, 1 : 1 (10, 17, 19). This means that the compatibility data are applicable if drugs are administered at the same infusion rate.
- Although the observation of the samples was carried out for 2 h, in a clinical setting, when two drugs are infused at 100 mL over 30 min, their contact time is 45 seconds. Even assuming that the 2 drugs are administered very slowly (at a rate of 100 mL/h), their contact time from the Y connector to the vascular access is 1.5 minutes, as the average volume of the

vascular line below the connector is 5 mL. For this reason, in this type of research, drug stability testing in the presence of a second infusion solution is omitted (17, 19, 20, 28-30, 34).

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Conflict of interest

The authors declare no conflict of interest.

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